The Institute of Paper Chemistry

Appleton, Wisconsin

Doctor's Dissertation

Effect of a 2-*O*-Acetyl Substituent on the Stereoselectivity of Koenigs-Knorr Reactions Involving 1,2-*cis*-Glucopyranosyl Bromides

Jerry E. Wallace

June, 1975

EFFECT OF A 2-O-ACETYL SUBSTITUENT ON THE STEREOSELECTIVITY OF KOENIGS-KNORR REACTIONS INVOLVING 1,2-CIS-GLUCOPYRANOSYL BROMIDES

A thesis submitted by

Jerry E. Wallace

B.S. 1968, SUNY College of Forestry

M.S. 1973, Lawrence University

in partial fulfillment of the requirements
of The Institute of Paper Chemistry
for the degree of Doctor of Philosophy
from Lawrence University,
Appleton, Wisconsin

June, 1975

TABLE OF CONTENTS

ABSTRACT

Reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide and the 2-O-acetyl analog with cyclohexanol in the presence of $Hg(CN)_2$ in nitromethane-benzene (1:1, vol.) were investigated. Primary emphasis was on reactions at 10°C having a concentration ratio of 15:1:1 [ROH:RBr:$Hg(CN)_2$; RBr, ca. 6×10^{-3}M]. However, the effects of the reaction temperature (2-25°C) and the concentrations of the reactants were also studied. Products were measured quantitatively by GLC, and initial rates were determined by polarimetric analyses.

Under all conditions employed, the 2-O-acetyl derivative selectively formed the β-glucoside (93-98% of the glucosidic product). In contrast, the reaction of the 2-O-methyl derivative was less selective (73-82% β-glucoside), and the selectivity was significantly dependent on the alcohol concentration and the reaction temperature.

Both glucosyl bromide reactions exhibited first-order kinetic dependence on the glucosyl bromide and $Hg(CN)_2$ concentrations but not on the alcohol concentration. Thus, it is concluded that the reactions occur by a Lewis acid-catalyzed unimolecular mechanism in which the rate-determining step is heterolysis of the carbon-bromine bond, assisted by the $Hg(CN)_2$.

The observed autocatalysis indicates that other acids are formed which also assist in heterolysis of the carbon-bromine bond. These species could include HgCNBr, $HgBr_2$, HCN, HBr, and H^+, all of which can potentially be formed by the reaction of $Hg(CN)_2$ with bromide ion. It was shown that $HgBr_2$ is a more effective catalyst for the reactions than $Hg(CN)_2$.

For both reactions the initial mole ratio of β-glucoside increased as the alcohol concentration was increased, indicating that the departing anion

partially shielded the α-side of the carbonium ion from reaction with the alcohol. Therefore, glucoside formation occurred as the result of reaction of the alcohol with either the ion pair to give β-glucoside or the free carbonium ion to give α- and β-glucosides.

In addition, an intermediate, shown to be 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose, was partially responsible for formation of glucosides in the 2-O-acetyl substituted bromide reaction. Reaction of the C-2 acetoxy carbonyl oxygen with the carbonium ion and subsequent reaction of the resultant 1,2-dioxolenium ion with the alcohol yielded the orthoester. Supporting evidence for the formation of an orthoester intermediate was obtained by NMR analysis of an analogous reaction employing ethanol in which 1,2-O-(1-exo-ethoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose was detected.

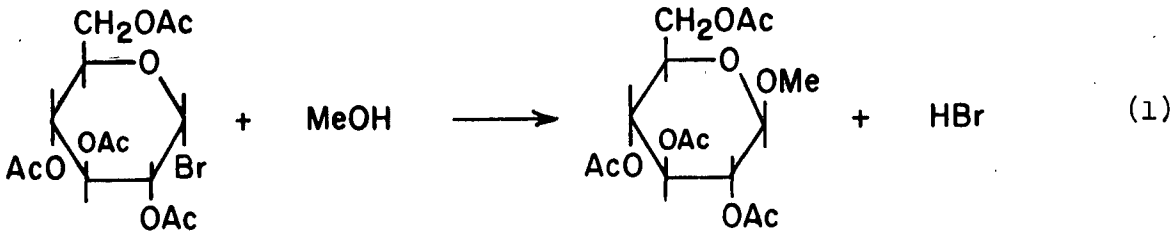
The reaction of the 2-O-acetyl substituted bromide in the presence of HgO, added to neutralize any acids formed and thereby stabilize the orthoester, yielded ca. 45% orthoester. In addition, the orthoester did react with cyclohexanol in the presence of $Hg(CN)_2$ and HBr to selectively form the β-glucoside. Thus, ca. 45% of the glucoside formation in the 2-O-acetyl bromide reaction occurred via the orthoester intermediate.

Initial product distributions indicated that the 2-O-acetyl carbonyl oxygen reacted five times faster with the α-side of the carbonium ion than did the alcohol. This and the fact that the orthoester intermediate selectively formed the β-glucoside were the main reasons for the high degree of stereoselectivity observed in the 2-O-acetyl substituted bromide reaction.

INTRODUCTION

THE KOENIGS-KNORR REACTION[1]

The Koenigs-Knorr reaction, in which a substituted glycosyl halide is reacted with an alcohol or a phenol, e.g., Equation (1), is one of the most useful methods for the synthesis of glycosides, disaccharides, and oligosaccharides. In addition to the reactants, the reaction often involves the use of a promoter[2], a desiccant, and an inert solvent.



(1)

The function of the promoter can be to neutralize or partially neutralize the acid produced by the reaction and thereby reduce the probability of acid-catalyzed deesterification and anomerization (1). Some promoters are used alone, e.g., mercuric cyanide (7) and cadmium carbonate (8), while with others a cocatalyst is often used, e.g., iodine with silver oxide (9) and mercuric bromide with mercuric oxide (10).

As some of the promoters neutralize the acid, water is produced, e.g., Equation (2).

$$2HBr + AgO \longrightarrow 2AgBr + H_2O \qquad (2)$$

If allowed to remain in the system, the water will compete with the alcohol for the glycosyl halide, resulting in the formation of a reducing sugar. Therefore,

---

[1] More extensive reviews on the Koenigs-Knorr reaction are given elsewhere (1-6).

[2] The term "promoter" will be used in place of the more commonly used term "acid acceptor."

a desiccant, e.g., Drierite ($CaSO_4$), is often employed to reduce the extent of this side reaction.

For simple alcohols, e.g., methanol, the alcohol can be employed as the solvent for the reaction[1]. However, for the preparation of glycosides from larger alcohols and for the synthesis of disaccharides or oligosaccharides, an inert solvent, e.g., chloroform, is normally used.

Glycosyl bromides or chlorides are generally used in Koenigs-Knorr reactions. Iodides are too unstable (reactive), while fluorides are generally too stable for practical use (4).

STATEMENT OF THE PROBLEM

Although the use of the Koenigs-Knorr reaction has been greatly extended since its discovery in the early 1900's (11), many factors which affect the steric course of this reaction are not clearly understood. This has, in certain cases, limited its value for the preparation of certain glycosides, disaccharides, and oligosaccharides. The purpose of this thesis was to investigate one of these factors: the effect of a C-2 O-acetyl substituent on the stereoselectivity of Koenigs-Knorr reactions involving 1,2-*cis*-glucopyranosyl halides.

Various studies of Koenigs-Knorr reactions involving 1,2-*cis*-glucopyranosyl halides have clearly demonstrated the effect of a C-2 O-acetyl substituent on the steric course of a reaction. Reactions of 1,2-*cis*-glucopyranosyl halides having a C-2 O-acetyl substituent are normally very stereoselective and occur predominantly with inversion of configuration at C-1 (4,12,13).

---

[1]The terms alcoholyses or solvolyses are generally used to denote these reactions.

In contrast, the steric course of reactions involving 1,2-cis-glucopyranosyl halides with a "nonparticipating" C-2 substituent is extremely variable and can range from predominately inversion of configuration at C-1 to predominately retention of configuration at C-1 (14-16).

Recently the reactions of cyclohexanol with 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide and the 2-O-acetyl analog employing various promoters and alcohol concentrations were investigated (17). The results of the investigation are presented in Table I. The 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reactions occurred with a high degree of inversion at C-1, essentially independent of the promoter employed or the alcohol concentration, whereas, the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reactions occurred with varying degrees of stereoselectivity, dependent both on the promoter employed and the alcohol concentration. These results further demonstrate the significant effect of a C-2 O-acetyl substituent on the stereoselectivity of Koenigs-Knorr reactions involving 1,2-cis-glucopyranosyl halides.

Frush and Isbell (18-20) originally proposed that the reason for the high degree of stereoselectivity observed in Koenigs-Knorr reactions of 1,2-cis-O-acetyl-glucopyranosyl halides was that these reactions occur by an S_N2 mechanism. More recent kinetic studies (21-27) have shown that reactions of glycosyl halides normally occur by an S_N1 mechanism. Only with extreme conditions, e.g., in a poorly solvating medium and/or a very strong nucleophile, do some of these reactions occur by an S_N2 mechanism.

Because of this, it has been postulated (13) that the main reason for the effect of a C-2 carboxylic ester substituent is direct participation by

TABLE I

REACTION OF CYCLOHEXANOL WITH 3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDES[a] AT 23°C (17)

Promoter	Alc.:Bromide[b] Mole Ratio	Mole Fraction β-Anomer[c]	
		2-O-Acetyl	2-O-Methyl
Ag_2O[d]	3	0.98	0.91
HgO[e]	3	0.96	0.82
$CdCO_3$[f]	3	0.98	0.53
$Hg(CN)_2$[g]	3	0.95	0.71
$Hg(CN)_2$[g]	10	0.95	0.81
$Hg(CN)_2$[g]	30	0.96	0.88

[a] Powdered Drierite was used as a desiccant in each reaction.

[b] Glucopyranosyl bromide concentration ranged from 0.061-0.066 molar.

[c] Mole fraction of β-anomer in the glucosidic products of the reactions of the 2-O-acetyl substituted glucosyl bromide and the 2-O-methyl substituted glucosyl bromide.

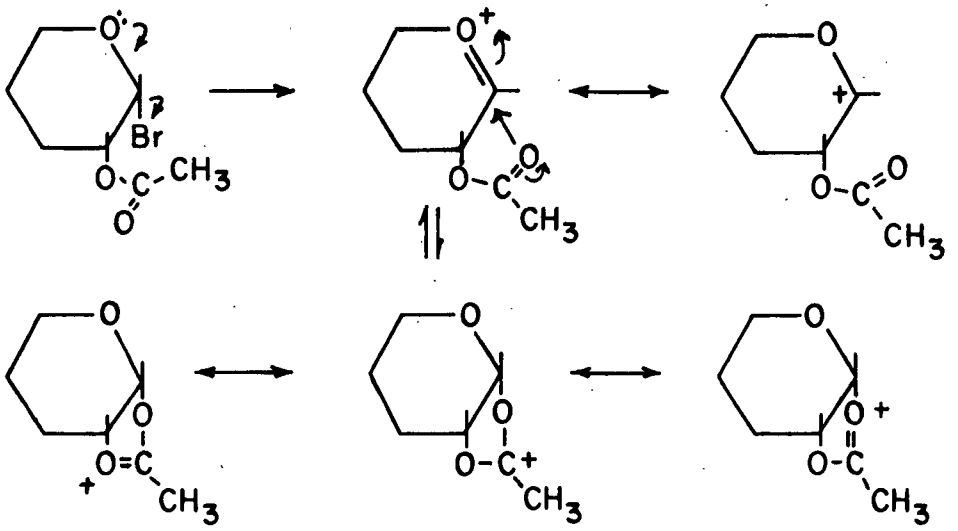
[d] Solvent, chloroform; cocatalyst, I_2

[e] Solvent, chloroform; cocatalyst, $HgBr_2$.

[f] Solvent, toluene.

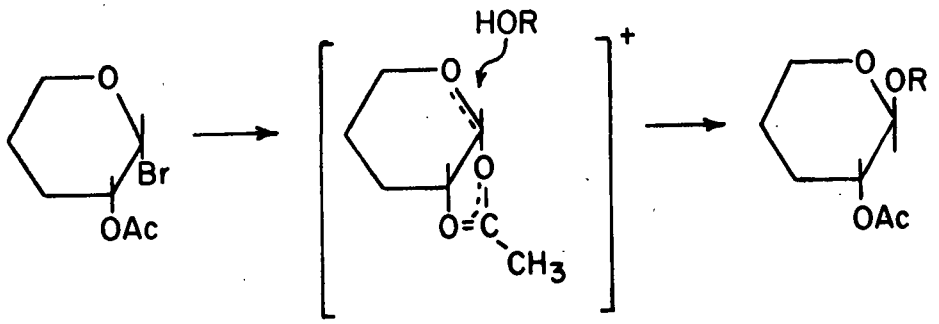
[g] Solvent, 1:1 nitromethane-benzene.

the substituent through the formation of a 1,2-dioxolenium ion as shown in Equation (3)[1].



(3)

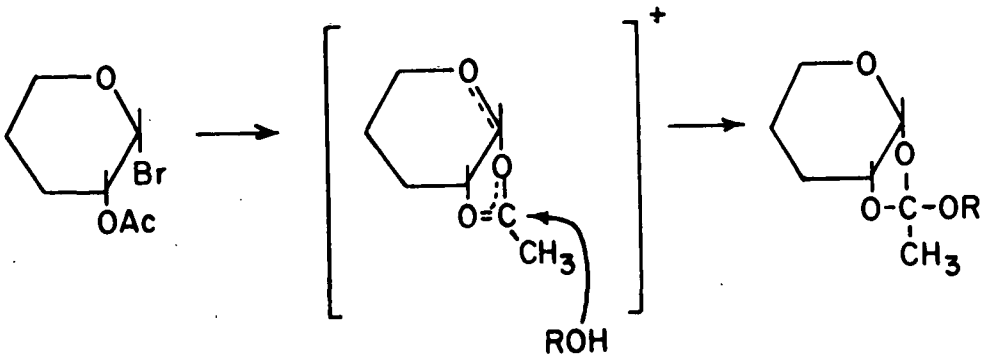
According to this hypothesis, the formation of the 1,2-dioxolenium ion has two effects: (1) it provides a more stable intermediate ion and (2) it directs the incoming nucleophile into the 1,2-trans position, Equation (4), thus resulting in a high degree of stereoselectivity.



(4)

[1]In this equation and subsequent equations depicting pyranoid rings, the 3, 4, and 5 substituents are not shown.

The validity of this explanation for the effect of a C-2 carboxylic ester is questionable. In the case of a 1,2-trans-O-acetyl-glucopyranosyl halide, the 2-O-acetyl substituent is sterically situated such that its carbonyl oxygen atom can aid in the displacement of the halogen atom with concomitant formation of a 1,2-dioxolenium ion (18-20). The 1,2-dioxolenium ion can subsequently react with the alcohol to yield an orthoester as one of the main products of the reaction if an acid acceptor is employed (2,4,18-20,28). Thus, if 1,2-dioxolenium ions are formed in reactions of 1,2-cis-O-acetyl glucopyranosyl halides, the alcohol should react with the dioxolenium ions as shown in Equation (5) to yield stable orthoesters.



(5)

Since orthoesters are normally not one of the observed products in these reactions, either the 1,2-dioxolenium ions are not formed or the orthoesters must act as intermediates for the subsequent formation of glucosides.

However, no one has demonstrated that an orthoester acts as an important intermediate for glucoside formation under typical Koenigs-Knorr reaction conditions. In fact, Rudie (3) has shown that glucoside formation from a carbohydrate orthoester in the presence of an acid acceptor is a very slow reaction.

This thesis was undertaken in an effort to ascertain the reason for the effect of a 2-O-acetyl substituent on the stereoselectivity of Koenigs-Knorr reactions involving 1,2-cis-glucopyranosyl halides.

SYSTEMS SELECTED FOR STUDY

The reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide and the 2-O-acetyl analog with low concentrations of cyclohexanol and promoted by mercuric cyanide were investigated. The reactions were conducted in nitromethane-benzene (1:1, vol.) which is often used as the solvent when mercuric cyanide is used in a Koenigs-Knorr reaction.

Mechanistic studies of Koenigs-Knorr reactions have been limited mainly to alcoholyses not involving a promoter. This is primarily due to the fact that the heterogeneous nature of reactions employing insoluble promoters make it difficult to obtain kinetic measurements. Mechanistic studies of these reactions have generally consisted of reconciling the products with the postulated mechanism. In this investigation mercuric cyanide was chosen as the promoter because its solubility in 1:1 nitromethane-benzene made it possible to obtain homogeneous reaction mixtures on which kinetic studies could be conducted. Hence, both kinetic measurements and product analyses could be used to diagnose the reaction mechanisms.

Cyclohexanol was used as the alcohol to approximate Koenigs-Knorr disaccharide syntheses and yet avoid the possible complicating effects that a substituted glycose could present in analysis of the reactions. In certain reactions, e.g., when kinetic data were not needed, Drierite was used as a desiccant.

For most of the reactions, the concentration ratio of cyclohexanol: glucosyl bromide:mercuric cyanide was 15:1:1[1]. This ratio, of course, was varied to determine the kinetic dependence on each of the reactants.

[1]Glucosyl bromide concentration, ca. 6×10^{-3}M.

RESULTS AND DISCUSSION

GENERAL

This investigation was concerned primarily with determining (1) whether an orthoester is involved in the formation of glucosides in the reaction of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide, (2) if changing the C-2 substituent of the 3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide from an acetoxy to a methoxy group changes the reaction mechanism, and (3) if the reactions exhibit kinetic dependence on the mercuric cyanide. As stated in the Introduction, formation of a 1,2-dioxolenium ion in the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction should lead to the formation of an orthoester, 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose. Hence, the detection of this orthoester could be used to determine the importance of direct participation by the 2-O-acetyl substituent during the course of the reaction.

Additional information concerning the mechanisms of the glucosyl bromide reactions was obtained by a kinetic study. The study included determination of the kinetic dependence of the reactions on the glucosyl bromide, the cyclohexanol, and the mercuric cyanide concentrations and calculation of thermodynamic functions of activation for each reaction.

2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE REACTION

GENERAL

The reaction scheme shown in Fig. 1 represents the overall reaction of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide in 1:1 nitromethane-benzene. The

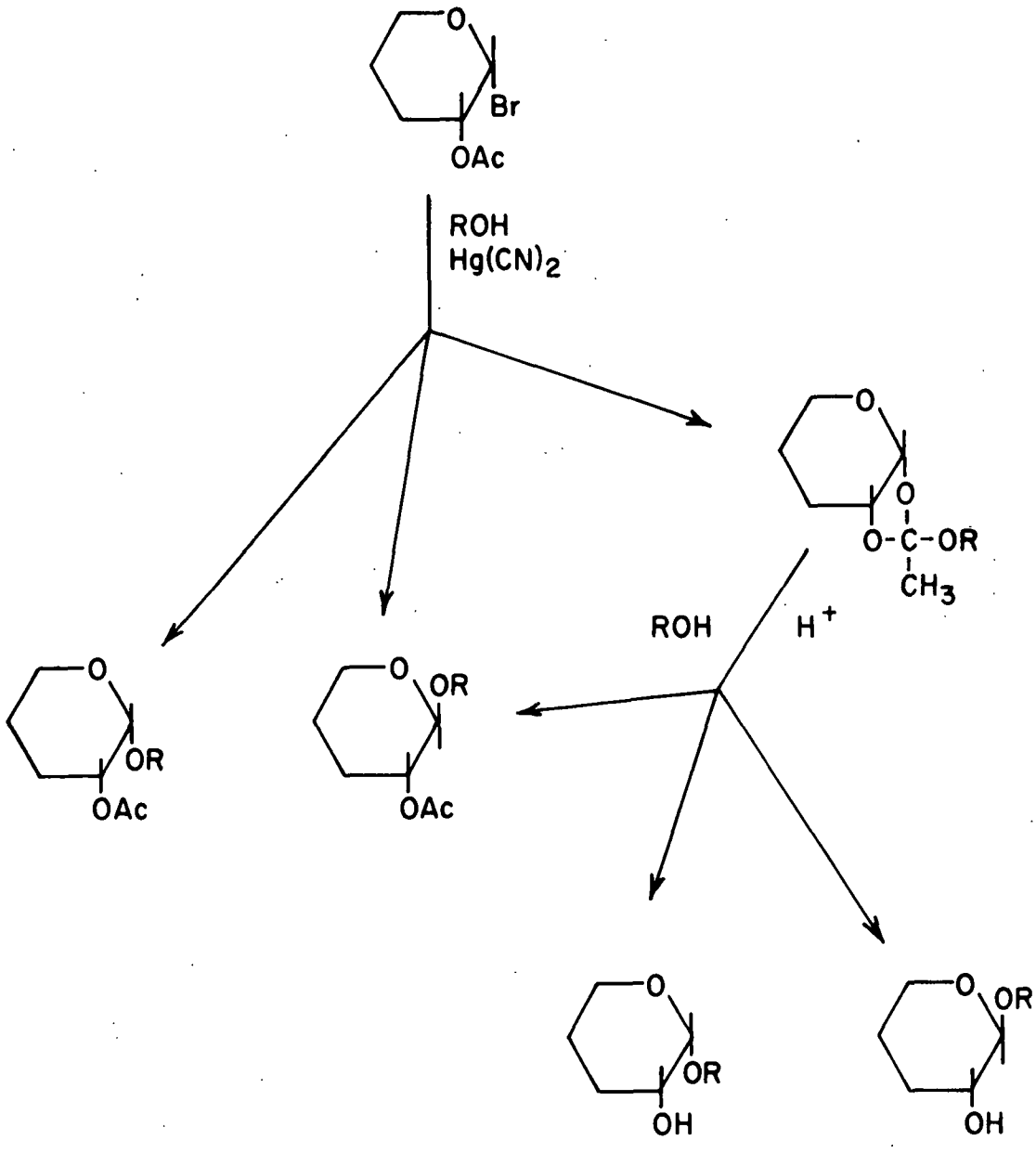


Figure 1. Overall Reaction of 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide with Cyclohexanol in the Presence of Mercuric Cyanide. (The 3, 4, and 5 Substituents of the Pyranoid Rings are not Shown.)

reaction resulted in the formation of cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α- and -β-D-glucopyranoside and 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose. The orthoester was a meta-stable intermediate which subsequently reacted with cyclohexanol to give cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside and cyclohexyl 3,4,6-tri-O-methyl-α- and -β-D-glucopyranoside. This description resulted from studies of the reaction by quantitative gas-liquid chromatography (GLC), polarimetry, and nuclear magnetic resonance spectrometry (NMR).

FORMATION OF 1,2-O-(1-CYCLOHEXOXYETHYLIDENE)-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSE

Evidence for the formation of 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose in the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction is based on: (1) the product distribution (obtained by GLC analyses) of this reaction as a function of time and (2) NMR analyses of analogous reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with ethanol in the presence of mercuric cyanide. In addition, the formation of cyclohexyl 3,4,6-tri-O-methyl-D-glucopyranosides, unsubstituted at OH-2, in the reaction is indicative of the formation of an orthoester intermediate.

The product distribution of the reaction of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol as a function of time is given in Table II and shown in Fig. 2. Note that as the glucosyl bromide disappeared, three compounds were formed[1]: cyclohexyl

[1]Three compounds were detected in addition to the hydrolysis product, 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose, which resulted from trace amounts of water in the system. Because the hydrolysis product was the result of an undesirable side reaction, its presence will be noted but it will not enter into the discussion.

2-O-acetyl-3,4,6-tri-O-methyl-α- and -β-D-glucopyranoside and 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose. The concentration of orthoester initially increased, but when the glucosyl bromide was essentially depleted the orthoester concentration decreased with a concurrent increase in the concentration of the cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside.

TABLE II

REACTION OF 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOSYL BROMIDE WITH CYCLOHEXANOL IN THE PRESENCE OF MERCURIC CYANIDE AT 10°C[a]

Time, min	Reactant[b]	Products[b,c]				
	Glucosyl Bromide	OE	Hydrolysis Product	α-Cyc 2-OAc	β-Cyc 2-OAc	Total Measured
15	0.96	0.02	Trace	Trace	0.03	1.01
30	0.88	0.05	0.01	0.01	0.07	1.02
51	0.76	0.10	0.01	0.02	0.15	1.04
71	0.54	0.14	0.01	0.02	0.33	1.04
80	0.37	0.16	0.02	0.03	0.47	1.05
90	0.22	0.17	0.02	0.03	0.59	1.03
100	0.12	0.20	0.02	0.04	0.68	1.06
120	0.02	0.21	0.02	0.05	0.74	1.04
180	--	0.10	0.03	0.05	0.83	1.01

[a] Reaction composition: glucosyl bromide, 5.451×10^{-3} M; cyclohexanol, 9.962×10^{-2} M; mercuric cyanide, 6.161×10^{-3} M; Drierite, 1.0 g; solvent, 1:1 nitromethane-benzene.

[b] Mole fraction of original reactant. Analyses of samples containing known concentrations of these compounds indicated that the mole fraction of each compound could be determined within ±2 mole%.

[c] See Nomenclature for compound names.

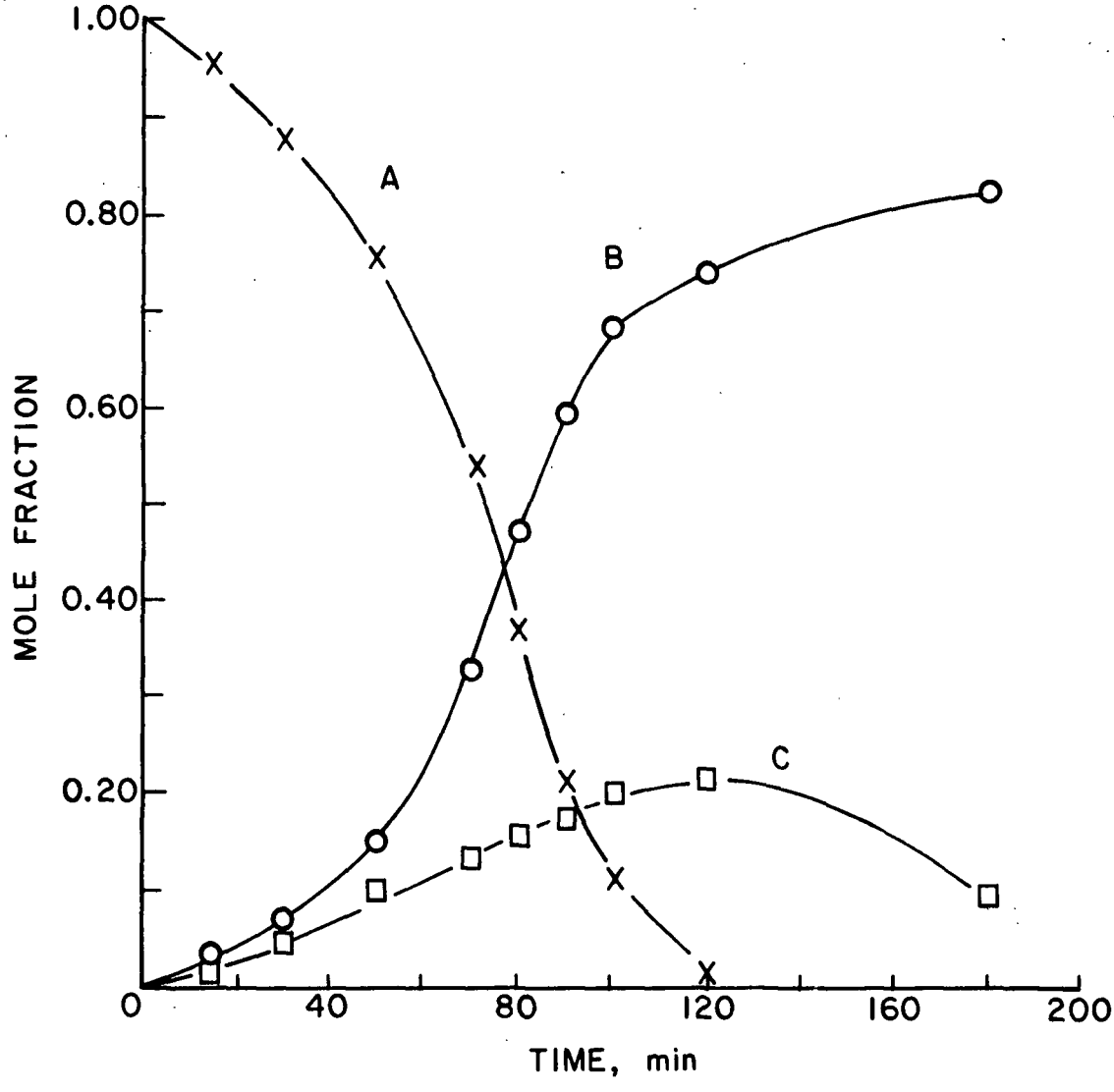


Figure 2. Reaction of 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide with Cyclohexanol in the Presence of Mercuric Cyanide: A, 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide; B, Cyclohexyl 2-O-Acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside; C, 1,2-O-(1-Cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose

GLC analysis of the orthoester concentration was not a direct analysis procedure in that the orthoester was hydrolyzed and subsequently analyzed as the propionyl derivatives of 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose. Thus, it was desirable to use an analytical procedure in which an intermediate orthoester could be analyzed directly without chemical modification. Therefore, NMR was used to analyze the products of a reaction of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with ethanol in the presence of mercuric cyanide in 1:1 nitromethane-benzene.

Ethanol was used in place of cyclohexanol in the reaction because the broad cyclohexyl multiplet would tend to mask the orthoacetyl methyl singlet of 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose. Also, the reaction could not be followed directly by NMR because of the low concentrations that were used. Hence, it was necessary to conduct a large-scale reaction of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with ethanol. As the reaction neared completion, a solution of sodium methoxide and thiophenol in methanol was added to quench the reaction and stabilize the orthoester. The reaction was then concentrated *in vacuo* and analyzed in total by NMR. A partial NMR spectrum of the reaction is shown in Fig. 3.

The singlet at 1.67 ppm ($CDCl_3$) is indicative of the orthoacetyl methyl group of 1,2-O-(1-*exo*-ethoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose (29). The fact that this functional group was responsible for the singlet at δ1.67 ppm was substantiated as follows. Addition of 1,2-O-(1-*exo*-ethoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose to the sample resulted in an increase in the height of the singlet. Subsequent addition of D_2O and acid to hydrolyze any orthoester present eliminated the singlet.

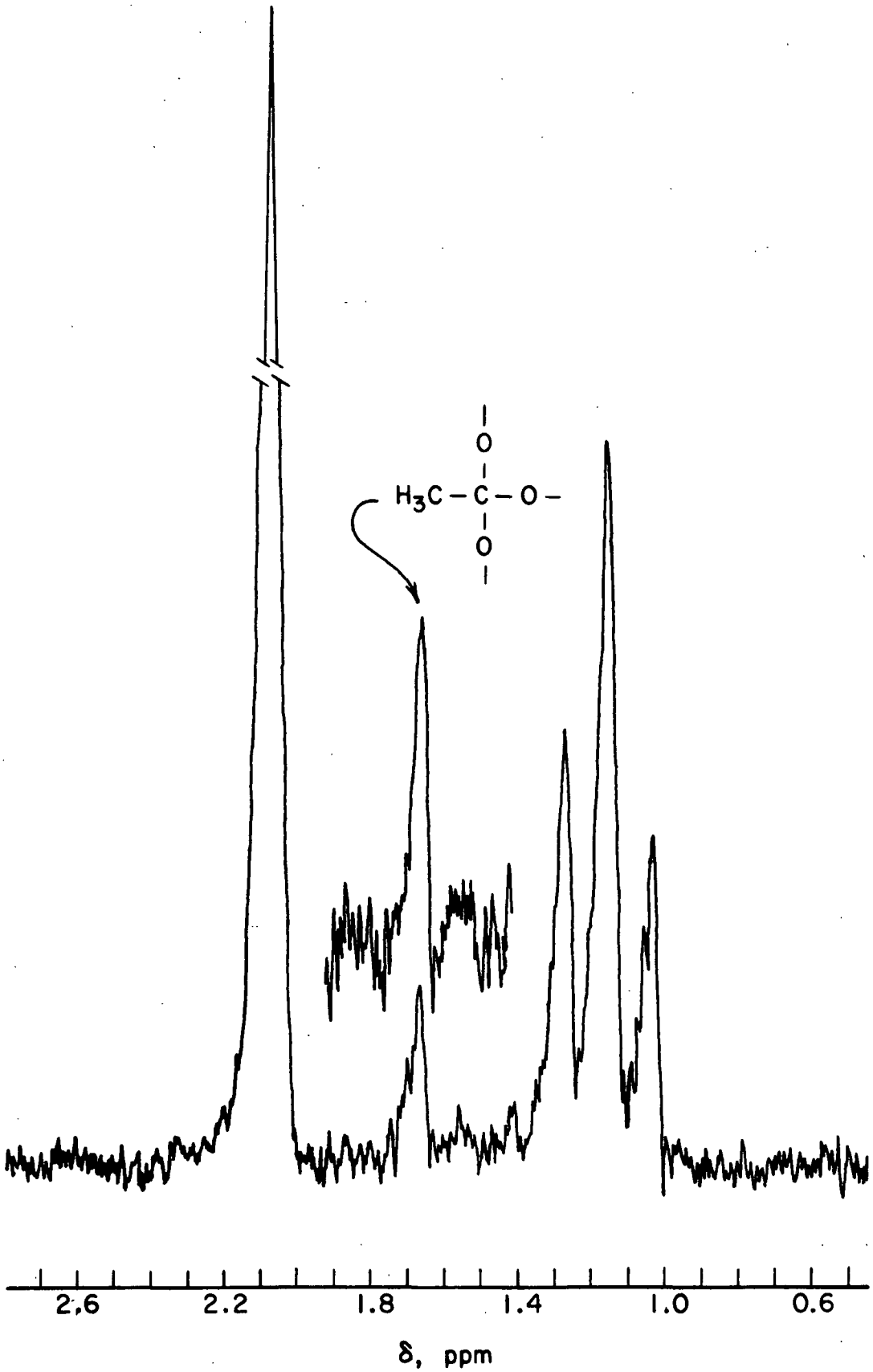


Figure 3. Partial NMR Spectrum ($CDCl_3$) of the Products of a Reaction of 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide with Ethanol in the Presence of Mercuric Cyanide

The final product distribution data for a reaction of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide, given in Table III, shows that the reaction resulted in the formation of small amounts (approximately 2%) of cyclohexyl 3,4,6-tri-O-methyl-D-glucopyranosides. The formation of these 2-hydroxyglucosides is indicative of the formation of an orthoester intermediate since these compounds are not formed directly from the glucosyl bromide. It is possible that these small amounts of 2-hydroxyglucosides could be the result of deacetylation of the cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranosides during the reaction. However, this is considered unlikely under the weakly acidic reaction conditions and the low alcohol concentrations employed. In addition, it will be shown that the reaction of the orthoester with the cyclohexanol leads to the formation of small amounts of 2-hydroxyglucosides.

POLARIMETRIC RATE DATA

Calculation of Reaction Rates from Polarimetry

The rates of glucosyl bromide disappearance in the reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide were determined from optical rotation-time data[1] and Equation[2](6):

$$H = H_o(\alpha_t - M)(\alpha_o - M)^{-1}, \qquad (6)$$

---

[1]Optical rotation-time data for reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide are given in Appendix II.

[2]Derivation given in Appendix III.

TABLE III

FINAL PRODUCT ANALYSIS[a] OF THE REACTION OF 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE WITH CYCLOHEXANOL IN THE PRESENCE OF MERCURIC CYANIDE AT 10°C[b,c]

Product[d]	Mole Fraction[e]
α-Cyc 2-OAc	0.05
β-Cyc 2-OAc	0.80
α-Cyc 2-OH	0.01
β-Cyc 2-OH	0.01
Hydrolysis product	0.15

[a] Reaction terminated after a minimum of 10 hr reaction time.

[b] Reaction composition: glucosyl bromide, 6.802×10^{-3} M; cyclohexanol, 8.944×10^{-2} M; mercuric cyanide, 5.986×10^{-3} M; solvent, 1:1 nitromethane-benzene.

[c] The final product distribution of additional 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reactions are given in Appendix I.

[d] See Nomenclature for compound names.

[e] Mole fraction based on reactant. Analyses of samples containing known concentrations of these compounds indicated that the mole fraction of each glucosidic product could be determined within ±2 mole%.

where H = the concentration of glucosyl bromide at time t

H_o = the initial concentration of glucosyl bromide

α_t = the optical rotation of the reaction system at time t

α_o = the initial optical rotation of the reaction system; determined by extrapolating the polarimetric data to zero time.

M is a calculated optical rotation related to the reaction products and is defined by Equation (7)[1]:

$$M = (H_o M_G/1000)(n_a[\alpha_a] + n_b[\alpha_b] + n_c[\alpha_c]), \qquad (7)$$

[1] Derivation given in Appendix III.

where M_G = the gram-molecular weight of the glucosides and the orthoester which is the same

n_a, n_b, n_c = the initial mole fraction[1], based on the products, of α-glucoside, β-glucoside, and orthoester, respectively

$[\alpha_a], [\alpha_b], [\alpha_c]$ = the specific optical rotation of the α-glucoside, β-glucoside, and orthoester, respectively

Equation (7) is based on the assumption that the reaction mixture contains only unreacted 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide, cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α- and -β-D-glucopyranoside, and 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose. It is known that hydrolysis, due to the presence of water in the reaction mixture, did occur. Hydrolysis of the orthoester yields 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose while hydrolysis of the glucosyl bromide yields 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose. Mutarotation of the reducing sugar may also have occurred. All of these complications made it impossible to obtain a specific optical rotation for the hydrolysis products which could have been used in Equation (7). Hence, it was assumed that the formation of hydrolysis products had a negligible effect on Equation (7). This assumption can be made because the contribution of the small amount of observed hydrolysis product (Table XXI) to M [Equation (7)] would be small. In addition, the value of M is much smaller than that of α_o[2] (or α_t in the initial portion of the reaction) and thus, small changes in M have a negligible effect on the value of H [Equation (6)].

---

[1]The initial mole fractions of α- and β-glucosides and orthoester were used in the calculation of M which was subsequently used to determine the initial reaction rate. The data in Table XX (Appendix I) show that these mole fractions were essentially time-independent during the early portion of the reaction.

[2]For most reactions, α_o equaled about 0.600 whereas the value of M was close to zero.

In order to evaluate M [Equation (7)], it was necessary to determine the specific optical rotations, $[\alpha_a]$, $[\alpha_b]$, and $[\alpha_c]$, and the initial mole fractions, n_a, n_b, and n_c for the reaction for which the initial rate was to be determined.

Specific Optical Rotations

Solutions of cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranoside, cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside, and 1,2-O-(1-exo-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose in 1:1 nitromethane-benzene were prepared. Since the temperature-volume relationships for 1:1 nitromethane-benzene were not known, solutions of each compound had to be prepared at every temperature for which the specific optical rotation was determined. Each solution was then transferred to a thermostatted polarimeter tube. Sufficient time was allowed for thermal equilibrium to take place in the polarimeter tube. The optical rotations were measured using a mercury lamp at 546.1 nm. These values are given in Table IV.

TABLE IV

SPECIFIC OPTICAL ROTATIONS OF 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE REACTION PRODUCTS IN 1:1 NITROMETHANE-BENZENE AS A FUNCTION OF TEMPERATURE

	$[\alpha]^t_{546.1}$			
Compound[a]	10°C	15°C[b]	20°C[b]	25°C
α-Cyc 2-OAc	186	(186)	(187)	187
β-Cyc 2-OAc	-25.1	(-24.4)	(-23.6)	-22.9
exo-OE[c]	47.8	(47.4)	(46.9)	46.5

[a] See Nomenclature for compound names.

[b] Calculated by assuming that the specific optical rotation is linearly dependent on temperature.

[c] exo-Isomer of the orthoester.

The specific optical rotations were measured at two temperatures, 10 and 25°C. For the other reaction temperatures (15 and 20°C), the specific optical rotations were calculated by assuming that the specific optical rotation is a linear function of temperature in this temperature range. This type of linear dependence has been reported previously for similar compounds (1,30,31).

Initial Product Distribution

Appendix I contains mole fractions, based on the reaction products, of cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranoside, cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside, and 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose in reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide employing various reaction temperatures, alcohol concentrations, mercuric cyanide concentrations, and glucosyl bromide concentrations. The mole fractions of α- and β-glucosides, and orthoester used in Equation (7) were determined by extrapolating the product distributions given in Appendix I to time zero. These extrapolated values are given in Table V.

Rate Equation

The initial distribution of products and their specific optical rotations were used to calculate M [Equation (7)] and subsequently the glucosyl bromide concentration, H, [Equation (6)], as a function of time. The glycosyl bromide concentration decreases with time (Fig. 4). The deviation from linearity, occurring at about 8 minutes, was due to autocatalysis in the reaction. The initial rate, $(dH/dt)_{t=0}$, was determined from the initial linear portion of the curve. In practice the curve of glucosyl bromide versus time was used only to determine when the initial portion of the curve deviated from

TABLE V

INITIAL PRODUCT DISTRIBUTIONS[a] USED FOR CALCULATING THE GLUCOSYL BROMIDE CONCENTRATIONS FROM POLARIMETRY FOR 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE REACTIONS[b]

Reaction[c] Number	Temp., °C	Glucosyl Bromide (10^3M)	ROH[d] (10^3M)	$Hg(CN)_2$ (10^3M)	Initial Distribution[a,e]		
					n_a	n_b	n_c
1	10	6.802	8.944	5.986	0.07	0.58	0.35
2	10	3.142	10.029	5.998	0.05	0.52	0.43
3	10	6.063	4.882	6.185	0.10	0.45	0.44
4	10	5.786	13.474	6.100	(0.05	0.70	0.25)[f]
5	10	6.320	18.253	5.839	0.04	0.82	0.14
6	10	6.158	9.465	2.981	0.07	0.59	0.35
7	10	5.852	8.990	12.083	0.06	0.58	0.36
8	25	4.405	6.541	4.523	0.08	0.58	0.40
9	20	4.328	6.957	4.408	(0.06	0.56	0.37)[g]
10	20	5.542	8.967	5.981	0.06	0.56	0.37
11	15	4.405	6.680	4.420	0.07	0.58	0.35
12	10	4.706	6.757	4.513	(0.07	0.58	0.35)[h]

[a] The mole fraction values n_a, n_b, and n_c, were determined by extrapolating the essentially linear GLC data for the reactions to time zero.

[b] Reactions of the glucosyl bromide with cyclohexanol in the presence of mercuric cyanide in 1:1 nitromethane-benzene.

[c] In reference to polarimetric data given in Appendix II.

[d] ROH = cyclohexanol.

[e] Initial mole fractions: n_a, cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranoside; n_b, cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside; n_c, 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose.

[f] Calculated from the values for Reactions 1 and 5 by assuming that a linear relationship exists between the mole fractions and the alcohol concentration.

[g] Assumed to be the same as Reaction 10.

[h] Assumed to be the same as Reaction 11.

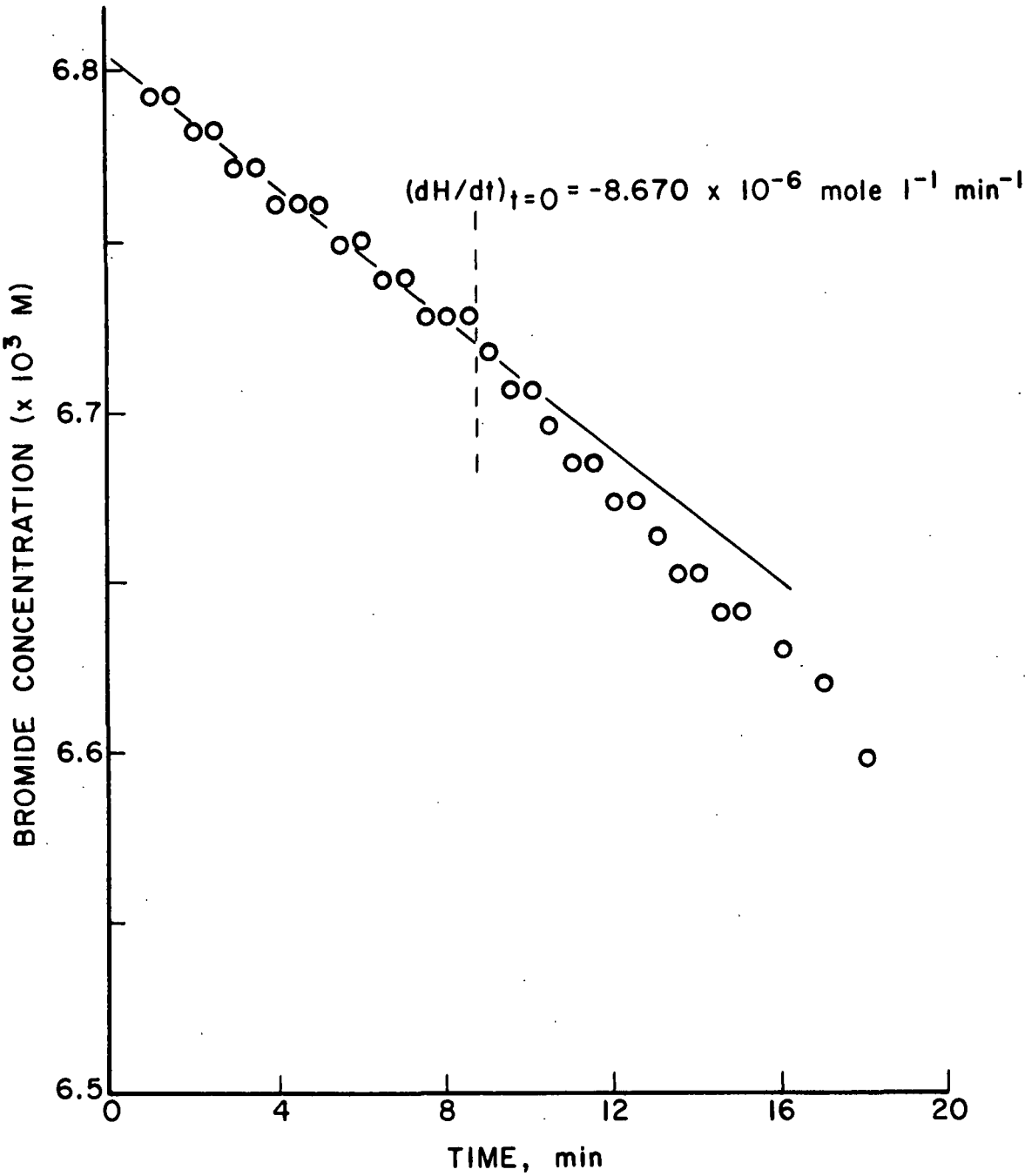


Figure 4. Plot of the Glucosyl Bromide Concentration Versus Time Determined from the Polarimetric Data of a Reaction of 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide with Cyclohexanol in the Presence of Mercuric Cyanide at 10°C

linearity. The initial rate was then calculated from the initial linear portion of the curve by the method of least squares.

The initial rates of reaction, obtained for a series of reactions in which the concentration of only one reactant at a time was varied, are given in Table VI. Log $(d\underline{H}/d\underline{t})_{\underline{t}=0}$ was plotted against log $[H]_{\underline{t}=0}$, log $[ROH]_{\underline{t}=0}$, and log $[Hg(CN)_2]_{\underline{t}=0}$ (see Fig. 5) according to the logarithmic form of the expression $d\underline{H}/d\underline{t} = -\underline{k}[H]^{\underline{a}}[ROH]^{\underline{b}}[Hg(CN)_2]^{\underline{c}}$, and it was determined that the initial rate of the reaction is proportional to $[H]^{0.97}$ and $[Hg(CN)_2]^{0.97}$ but independent of the cyclohexanol concentration. Therefore, the initial rate expression for this reaction is given by Equation (8):

$$(dH/dt)_{t=0} = -k[H][Hg(CN)_2], \qquad (8)$$

where $(d\underline{H}/d\underline{t})_{\underline{t}=0}$ = the initial rate of the reaction

$\underline{k}$ = the initial rate constant

$[H]$ = the concentration of glucosyl bromide

$[Hg(CN)_2]$ = the concentration of mercuric cyanide

The first-order dependence on the glucosyl bromide and the Lewis acid, mercuric cyanide, but not on the cyclohexanol indicates that the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reactions occur by a Lewis acid-catalyzed unimolecular type of mechanism. The rate-determining step of the reaction is heterolysis of the carbon-bromine bond, assisted by the mercuric cyanide, as shown in Equation (9).

TABLE VI

INITIAL RATES OF 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE REACTIONS AT VARIOUS CYCLOHEXANOL, GLUCOSYL BROMIDE, AND MERCURIC CYANIDE CONCENTRATIONS (10°C)[a]

Reaction Number	Glucosyl Bromide (10^3M)	Cyclohexanol (10^3M)	$Hg(CN)_2$ (10^3M)	Initial Rate[b] (10^7 mole l^{-1} sec^{-1})
1	6.802	8.944	5.986	1.54
2	3.142	10.029	5.998	0.75
3	6.063	4.882	6.185	1.42
4	5.786	13.474	6.100	1.46
5	6.320	18.253	5.839	1.48
6	6.158	9.465	2.981	0.78
7	5.852	8.990	12.083	3.16

[a] Solvent, 1:1 nitromethane-benzene.

[b] Initial reaction rates calculated from optical rotation-time data and Equation (6). The polarimetric data are in Appendix II.

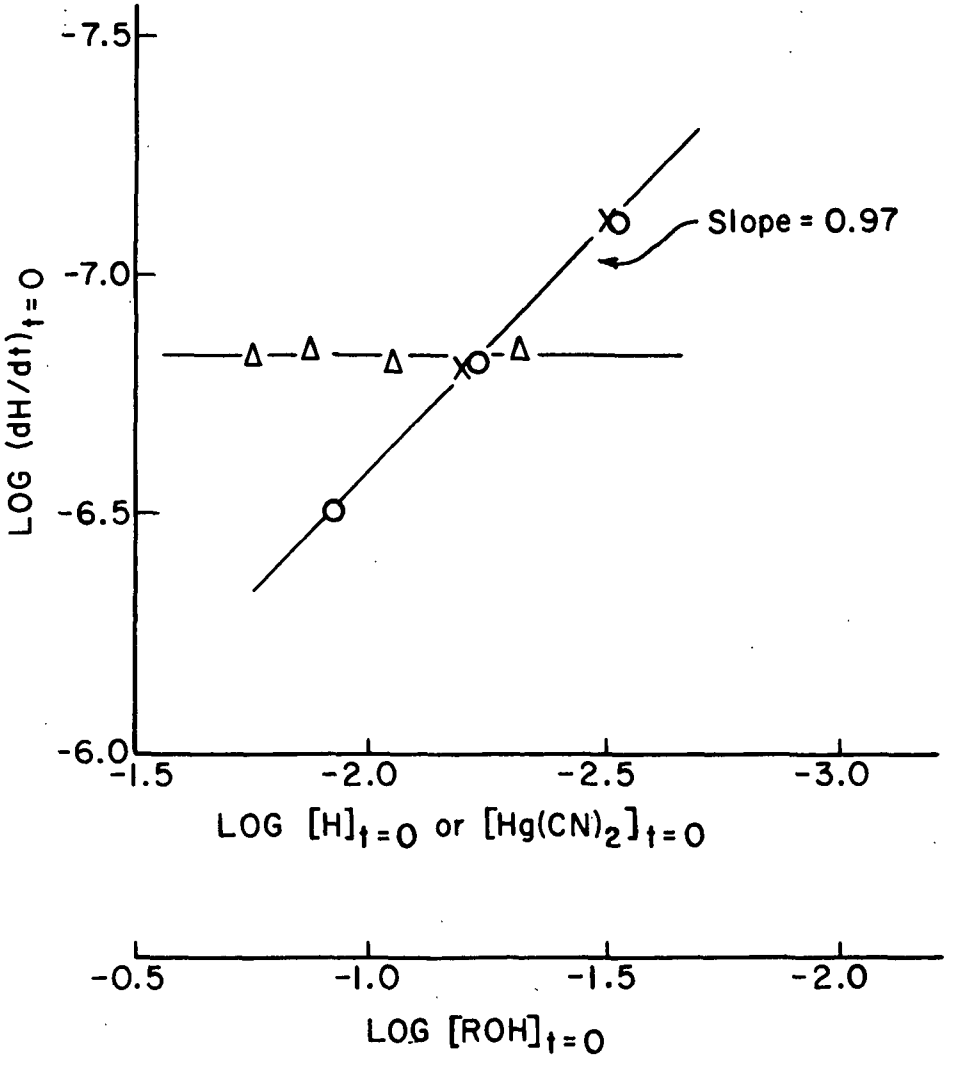
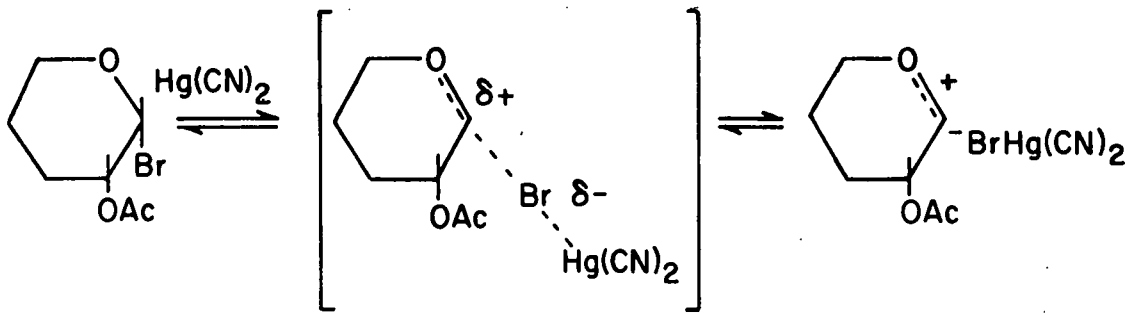


Figure 5. Plot of Log $(dH/dt)_{t=0}$ Versus Log $[H]_{t=0}$, Log $[Hg(CN)_2]_{t=0}$, and Log $[ROH]_{t=0}$ for 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide Reactions (10°C); o = $Hg(CN)_2$, x = RBr, Δ = ROH



(9)

The autocatalysis exhibited by the reaction is consistent with the mercuric cyanide reacting with the bromide ion, liberated from the glucosyl bromide, to form other Lewis acids which also catalyze the reaction. Thus, the general rate expression is given by Equation (10).

$$dH/dt = -\sum_{1}^{i} k_i[H][A_i]^{n_i} \qquad (10)$$

where k_i = the rate constant corresponding to the ith Lewis acid in the reaction system

$[A_i]$ = the concentration of the ith Lewis acid in the system

n_i = the kinetic order for the ith Lewis acid in the system

The autocatalysis in the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction is discussed in more detail in a following section.

PATHWAYS TO GLUCOSIDE FORMATION

Glucoside formation in the reaction of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide occurred by three pathways: (1) attack by the cyclohexanol on the ion pair formed from the glucosyl bromide, (2) attack by the cyclohexanol on the free carbonium ion, and (3) the reaction of the orthoester intermediate, 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose, with the

cyclohexanol. The relative importance of each pathway was dependent on the cyclohexanol concentration.

Ion Pair and Free Carbonium Ion

The kinetic measurements show that the initial rate of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction is independent of the cyclohexanol concentration. Therefore, heterolysis of the carbon-bromine bond occurred prior to attack by the cyclohexanol on the C-1. To ascertain whether the anion was completely dissociated from the carbonium ion prior to attack by the cyclohexanol, the dependence of the product distribution on the cyclohexanol concentration was examined. One would expect the initial anomeric ratio of glucosides to be independent of the cyclohexanol concentration if shielding by the departing anion did not play a role in the product determining step of the reaction.

Table VII gives the initial product distribution of several 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reactions in which only the cyclohexanol concentration was varied significantly. As the cyclohexanol concentration was increased, the initial mole fraction of β-glucoside increased while that of the α-glucoside and the orthoester decreased which indicates that the departing anion must have partially shielded the α-side of the C-1, or that these ions exist as an ion pair.[1]

An increase in the cyclohexanol concentration would increase the availability of the alcohol to attack the carbonium ion, and therefore, the probability that a nucleophilic substitution would take place prior to

[1]Whether the ions exist as an "intimate" ion pair or "solvent separated" ion pair (32,33) is not known.

dissociation of the ion pair would increase. Hence, shielding by the departing anion would become more important as the cyclohexanol concentration is increased which would lead to an increase in the mole fraction of β-glucoside and a decrease in the mole fraction of α-glucoside and orthoester.

TABLE VII

REACTION OF 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE (10°C)[a] — DEPENDENCE OF THE INITIAL PRODUCT DISTRIBUTION ON THE CYCLOHEXANOL CONCENTRATION

Glucosyl Bromide (10^3M)	Cyclohexanol (10^2M)	$Hg(CN)_2$ (10^3M)	Initial Mole Fraction[b] α-Cyc 2-OAc	β-Cyc 2-OAc	OE
6.063	4.882	6.185	0.10	0.45	0.44
6.802	8.944	5.986	0.07	0.58	0.35
6.320	18.253	5.839	0.04	0.82	0.14

[a] Solvent, 1:1 nitromethane-benzene.

[b] Mole fraction based on the products. Calculated by extrapolating the essentially linear GLC data to time zero. See Nomenclature for compound names.

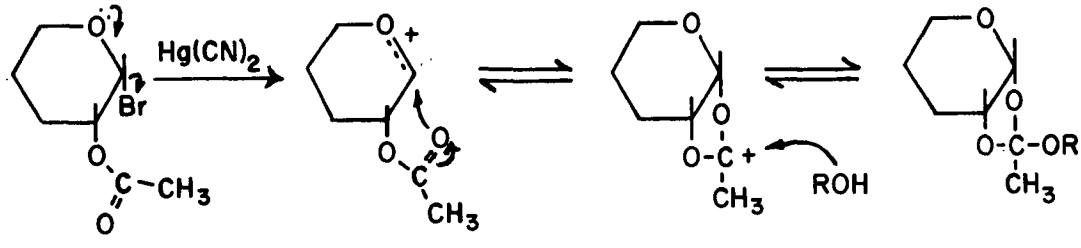
Attack by the cyclohexanol on the α-side of the C-1 is possible only if the C-1 is not shielded by the anion. Hence, formation of the α-glucoside is evidence that some of the ion pairs dissociate to form free carbonium ions. Ion exchange (α-ion pair $\overset{Br^-}{\rightleftharpoons}$ β-ion pair) (14,16) could account for the partial retention of configuration at C-1. However, if ion exchange were the reason for the partial retention of configuration at C-1, one would expect the initial mole fraction of α-glucoside in the reaction products to be zero. The data in Table VII show that this is not the case. Accordingly, it is believed that the α-glucoside formation occurred as a result of dissociation of the ion pair and not as a consequence of ion exchange.

In addition to the free carbonium ion forming the α-glucoside, it must also form some β-glucoside. The ratio of β-glucoside formed via the ion pair relative to that formed via the free carbonium ion is not known. It is known, however, that the degree of glucoside formation which occurred via the free carbonium ion was dependent on the cyclohexanol concentration.

It will be shown below that no cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranoside was formed from the reaction of the orthoester with the cyclohexanol. Hence, it is known that attack by the cyclohexanol on the α-side of the free carbonium ion is the only pathway to the formation of the α-glucoside.

Orthoester Intermediate

The free carbonium ion formed by the dissociation of the ion pair not only reacts with cyclohexanol but also is open for attack on the α-side by the carbonyl oxygen of the neighboring 2-O-acetyl substituent as depicted in Equation (11).



(11)

Subsequent reaction of cyclohexanol with the 1,2-dioxolenium ion would lead to the formation of 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose.

As discussed previously, the concentration of orthoester initially increased, but when the glucosyl bromide was essentially depleted, its concentration decreased with a concurrent increase in the concentration of the cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside (Table II, Fig. 2). These data indicate that the orthoester was an intermediate for glucoside formation. To obtain additional evidence for this, the reaction of 1,2-O-(1-exo-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose with cyclohexanol in the presence of mercuric cyanide in 1:1 nitromethane-benzene was investigated. The product distribution as a function of time for this reaction is given in Table VIII. Note that the rate of orthoester disappearance was very slow; after 72.5 hours, only 8% of the orthoester had reacted.

Based on the data of Table VIII, one would expect that the orthoester should be relatively stable in the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction system. The fact that it was not indicates that some species must have been formed by the reaction of the glucosyl bromide which catalyzed the reaction of the orthoester intermediate with the cyclohexanol. This species could have been HBr or possibly HCN.

Hydrogen bromide is a product of the reaction of the glucosyl bromide with the cyclohexanol. The addition of HBr to the reaction of 1,2-O-(1-exo-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose with cyclohexanol in the presence of mercuric cyanide greatly increased the rate of this reaction; after 90 minutes reaction time, the reaction was about 96% complete (Table IX). These data indicate that HBr could have catalyzed the reaction of the orthoester. The effectiveness of HBr as a catalyzing species, however, should have been reduced due to the presence of mercuric cyanide. Potentially, mercuric cyanide can react with HBr according to Equation 12 to form mercuric

TABLE VIII

REACTION OF 1,2-O-(1-EXO-CYCLOHEXOXYETHYLIDENE)-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSE WITH CYCLOHEXANOL IN THE PRESENCE OF MERCURIC CYANIDE AT 20°C[a]

Time, min	Reactant[b], OE	Products[b,c] TMG	β-Cyc 2-OAc	α-Cyc 2-OH	β-Cyc 2-OH	Total Measured
21	0.98	0.01	--	--	--	0.99
50	0.97	0.01	--	--	--	0.98
105	0.98	0.01	--	--	--	0.99
189	0.99	0.01	--	--	--	1.00
609	0.96	0.01	0.01	--	--	0.98
2070	0.92	0.02	0.02	Trace	0.01	0.97
4350	0.92	0.02	0.03	0.01	0.02	1.00

[a] Reaction composition: orthoester, 6.169×10^{-3}M; cyclohexanol, 9.009×10^{-2}M; mercuric cyanide, 5.969×10^{-3}M; Drierite, 1.0 g; solvent, 1:1 nitromethane-benzene.

[b] Mole fraction of original reactant. Analyses of samples containing known concentrations of these compounds indicated that the mole fraction of each glucosidic product could be determined within ±2 mole%.

[c] See Nomenclature for compound names.

bromide and the weaker acid, HCN (3). However, if formed, HCN should act similar to HBr in catalyzing the reaction of the orthoester intermediate with cyclohexanol.

$$Hg(CN)_2 + HBr \rightleftharpoons HgCNBr + HCN \qquad (12)$$

TABLE IX

REACTION OF 1,2-O-(1-EXO-CYCLOHEXOXYETHYLIDENE)-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSE WITH CYCLOHEXANOL IN THE PRESENCE OF MERCURIC CYANIDE AND HBr AT 10°C[a]

Time, min	Reactant[b], OE	Products[b,c] Hydrolysis Product	β-Cyc 2-OAc	α-Cyc 2-OH	β-Cyc 2-OH	Total Measured
10	0.91	N.D.[d]	0.07	Trace	Trace	0.98
20	0.77	N.D.	0.19	0.01	0.02	0.99
30	0.59	N.D.	0.38	0.02	0.02	1.01
40	0.43	N.D.	0.53	0.03	0.04	1.03
60	0.26	N.D.	0.67	0.04	0.04	1.01
90	0.04	0.08	0.78	0.04	0.05	0.99

[a] Reaction composition: orthoester, 5.031×10^{-3} M; cyclohexanol, 9.122×10^{-2} M; mercuric cyanide, 5.982×10^{-3} M; HBr, 5.987×10^{-3} M; Drierite, 1.0 g; solvent, 1:1 nitromethane-benzene.

[b] Mole fraction of original reactant. Analyses of samples containing known concentrations of these compounds indicated that the mole fraction of each glucosidic product could be determined within ±2 mole%.

[c] See Nomenclature for compound names.

[d] N.D. = not determined.

The data of Table IX show that the orthoester reacted with the cyclohexanol in the presence of mercuric cyanide and HBr to selectively form the 2-O-acetyl-β-glucoside (90% of the glucosidic product was cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside). These data are consistent with the product distribution data of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction, Table II, which indicates that a decrease in the orthoester concentration resulted primarily in an increase in the formation of the 2-O-acetyl-β-glucoside.

To determine how much of the glucoside formation occurred via the orthoester intermediate, mercuric oxide was added to the reaction of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide. Mercuric oxide should buffer any HBr or HCN produced by the reaction, e.g., Equation (13), and thereby stabilize the orthoester intermediate.

$$HgO + 2HX \longrightarrow HgX_2 + H_2O, \qquad (13)$$

where X = Br or CN. The product distribution as a function of time for the reaction of the glucosyl bromide with cyclohexanol in the presence of mercuric cyanide and mercuric oxide is given in Table X. Note that the amount of 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose formed remained essentially constant after the completion of the glucosyl bromide reaction indicating that the orthoester formed was stable under the conditions employed. Thus, the catalyzing species for the reaction must have been buffered.

Since the mercuric oxide did not significantly affect the product distribution (discussed below), it is possible through the use of the data given in Table X to compute the amount of β-glucoside formation which occurred via the orthoester intermediate for the reaction reported in Table II. This is graphically shown in Fig. 6. Curve A is taken from the data in Table II and represents the β-glucoside formed via the ion pair, free carbonium ion, and the orthoester intermediate. Curve B is the adjusted data[1] taken from

[1]The addition of mercuric oxide resulted in an increase in the rate of glucosyl bromide disappearance. Thus, it was necessary to adjust the data of Table X so that at any given time, the mole fractions of β-glucoside given by the two curves in Fig. 6 were for the same % reaction (glucosyl bromide) level.

Table X and represents the β-glucoside formed via the ion pair and free carbonium ion only since addition of mercuric oxide stabilized the orthoester formed in the reaction. The difference in the two curves (shaded area), therefore, represents the amount of β-glucoside formation which occurred via the orthoester intermediate for a reaction in which the concentration ratio of alcohol:glucosyl bromide:mercuric cyanide was about 15:1:1.

TABLE X

REACTION OF 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE WITH CYCLOHEXANOL IN THE PRESENCE OF MERCURIC CYANIDE AND MERCURIC OXIDE AT 10°C[a]

Time, min	Reactant[b], glucosyl bromide	Products[b,c] OE	Hydrolysis Product	α-Cyc 2-OAc	β-Cyc 2-OAc	Total Measured
15	0.95	0.02	--	--	0.04	1.01
31	0.85	0.06	--	0.02	0.09	1.02
60	0.46	0.22	0.01	0.05	0.27	1.01
91	0.12	0.40	0.02	0.06	0.41	1.01
120	0.02	0.45	0.02	0.07	0.47	1.03
150	--	0.46	0.03	0.07	0.49	1.05
180	--	0.46	0.05	0.06	0.48	1.05

[a]Reaction composition: glucosyl bromide, 5.368×10^{-3}M; cyclohexanol, 8.992×10^{-2}M; mercuric cyanide, 5.802×10^{-3}M; mercuric oxide, 1.163×10^{-2}M; Drierite, 1.0 g; solvent, 1:1 nitromethane-benzene.

[b]Mole fraction of original reactant. Analyses of samples containing known concentrations of these compounds indicated that the mole fraction of each glucosidic product could be determined within ±2 mole%.

[c]See Nomenclature for compound names.

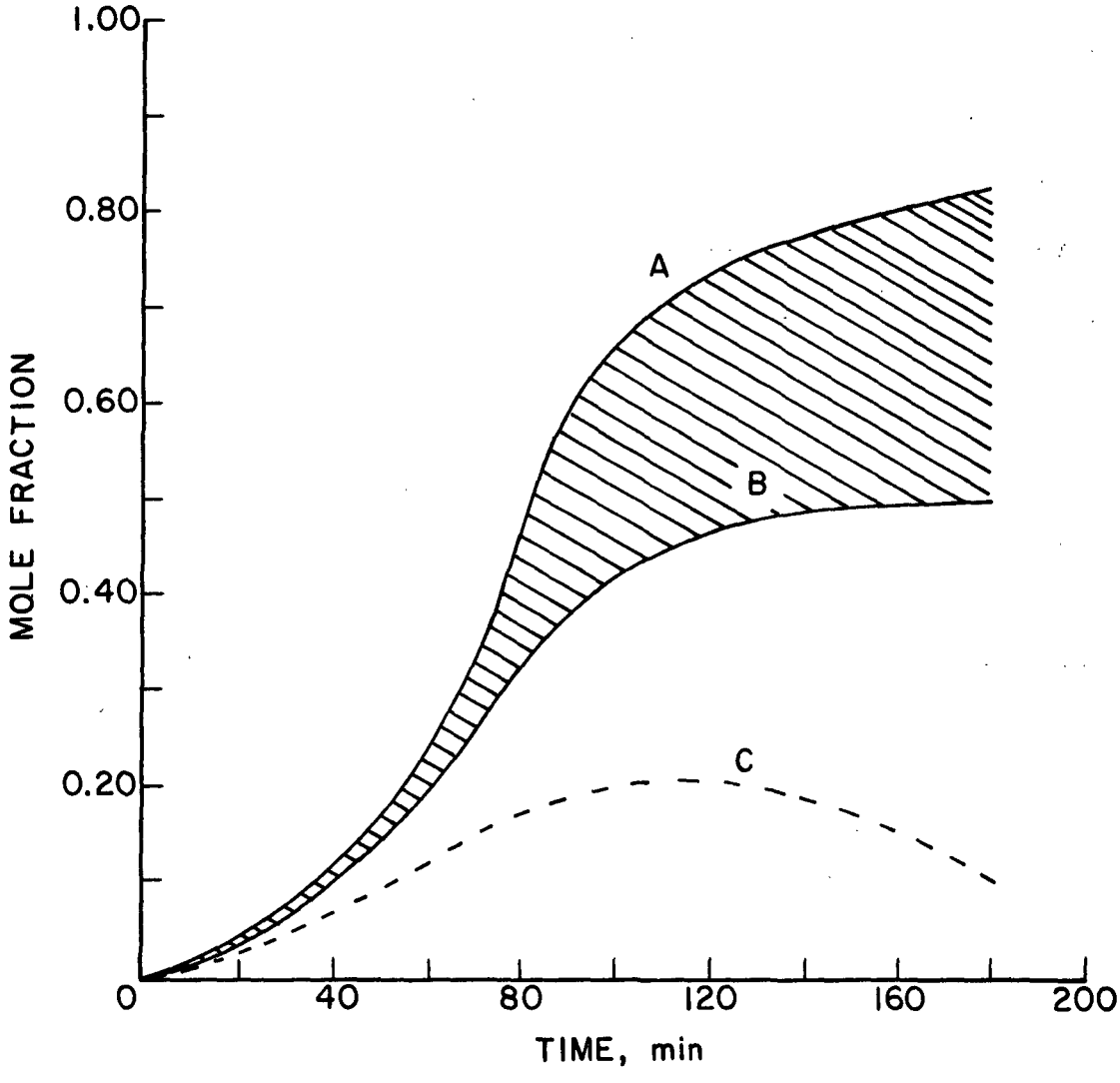


Figure 6. Reaction of 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide: A, Mole Fraction of β-Glucoside (Based on Reactant) Formed in the Reaction; Shaded Area (Between A and B), β-Glucoside Formed via the Orthoester Intermediate; B, Mole Fraction β-Glucoside Formed via the Ion Pair and Free Carbonium Ion; C, Mole Fraction of Orthoester in the Reaction Products

Figure 6 shows that most of the initial β-glucoside formation occurs via the ion pair and the free carbonium ion. As the concentration of orthoester increases, the amount of β-glucoside formed via the orthoester increases. Initially, the rate of orthoester formation appears to increase more rapidly than the rate of formation of β-glucoside via the orthoester. However, as the reaction proceeds, the rate of formation of β-glucoside via the orthoester increases significantly.

The data in Table X show that with an alcohol:glucosyl bromide:mercuric cyanide ratio of 15:1:1 and in the presence of mercuric oxide, about 45% of the glucosyl bromide reacted to form 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose. Again, assuming that the mercuric oxide did not have a significant effect on the product distribution, this finding indicates that under the same conditions, about 45% of the glucoside formation in the reaction of the glucosyl bromide with cyclohexanol in the presence of mercuric cyanide occurred via the orthoester intermediate. The remainder of the glucoside formation occurred as a result of attack by the cyclohexanol on the ion pair or the free carbonium ion.

To check the assumption that the presence of mercuric oxide did not significantly change the product distribution, the initial product distribution of the reaction involving mercuric oxide was compared to that of the reaction conducted under the same conditions except with no mercuric oxide added. This comparison, given in Table XI, indicates that mercuric oxide did not significantly affect the product distribution of the reaction.

The product distribution of the reaction of 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose with cyclohexanol in the presence of

mercuric cyanide and HBr (Table IX) shows that cyclohexyl 3,4,6-tri-O-methyl-α- and -β-D-glucopyranoside accounted for about 9% of the reaction product. Based on this, if 45% of the glucoside formation in the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction[1] occurs via the orthoester intermediates, then one would expect about 4% of the glucosyl bromide reaction product to be cyclohexyl 3,4,6-tri-O-methyl-D-glucopyranoside. The final product results given in Table III show that approximately 2% of the glucosyl bromide reaction product is cyclohexyl 3,4,6-tri-O-methyl-D-glucopyranoside.

TABLE XI

INITIAL PRODUCT DISTRIBUTIONS FOR REACTIONS OF 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE WITH CYCLOHEXANOL IN THE PRESENCE OF MERCURIC CYANIDE WITH AND WITHOUT THE ADDITION OF MERCURIC OXIDE (10°C)

Products[a]	Initial Mole Fraction[b] HgO Added[c]	Initial Mole Fraction[b] Without HgO[d]
OE	0.36	0.35
α-Cyc 2-OAc	0.07	0.07
β-Cyc 2-OAc	0.57	0.58

[a] See Nomenclature for compound names.

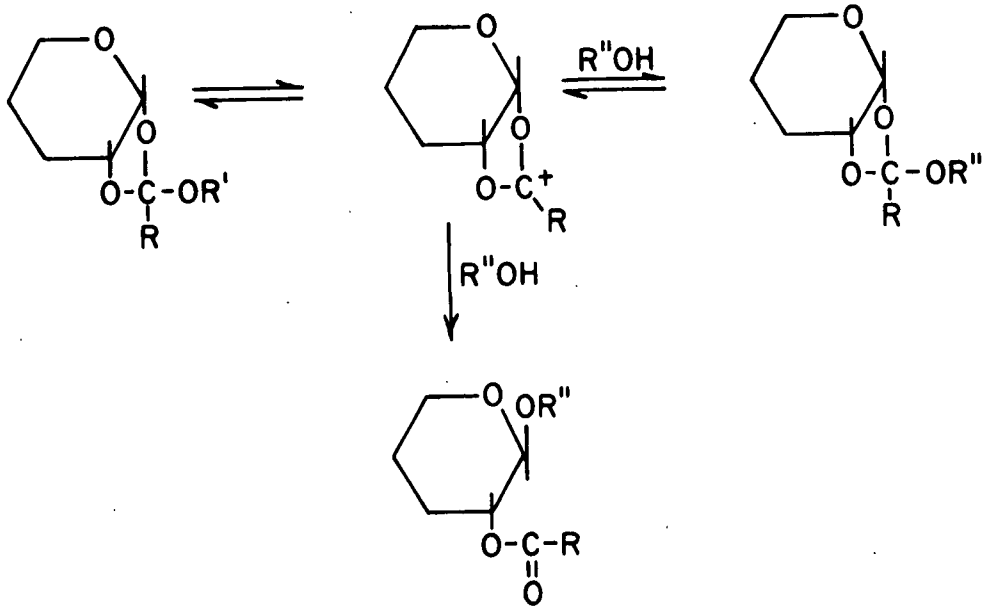
[b] Mole fractions based on products. Calculated by extrapolating the essentially linear GLC data to time zero.

[c] Reaction composition: glucosyl bromide, 5.368×10^{-3}M; cyclohexanol, 8.992×10^{-2}M; mercuric cyanide, 5.802×10^{-3}M; mercuric oxide, 1.163×10^{-2}M; Drierite, 1.0 g; solvent, 1:1 nitromethane-benzene.

[d] Reaction composition: glucosyl bromide, 5.451×10^{-3}M; cyclohexanol, 9.962×10^{-2}M; mercuric cyanide, 6.161×10^{-3}M; Drierite, 1.0 g; solvent, 1:1 nitromethane-benzene.

[1] Cyclohexanol:glucosyl bromide:mercuric cyanide concentration ratio of 15:1:1.

Based on the discussion given below, it is believed that glucoside formation (subsequent to reaction of the 2-O-acetyl carbonyl oxygen with the C-1 carbonium ion) occurred mainly as a result of the acid-catalyzed reaction of the orthoester with the cyclohexanol rather than nucleophilic attack at the anomeric carbon atom of the 1,2-dioxolenium ion by cyclohexanol. It has been proposed that glycoside formation from acid-catalyzed reactions of glycose 1,2-(alkyl orthoacylates) with alcohols occurs via the 1,2-dioxolenium ion as shown in Equation (14) (34).



(14)

However, this mechanism has been disputed recently (29,35) because it can only account for the formation of 1,2-trans-2-O-acyl-glucosides and not for the formation of such products as 1,2-cis-glycosides, 2-hydroxyglycosides, and 1,2-dihydroxyglycoses. In certain reactions, these latter compounds have been found to be important products.

Based on a mechanistic study of ethanolyses of 3,4,6-tri-O-methyl-1,2-O-(1-alkoxyethylidene)-α-D-glucopyranoses, Hultman (29) proposed a mechanism which accounts for all the products of acid-catalyzed reactions of glycose 1,2-(alkyl

orthoacetates). The mechanism involved two phases: (1) alkoxy exchange and (2) glycoside formation. Alkoxy exchange which was rapid compared to glycoside formation, was postulated to occur via the 1,2-dioxolenium ion and was accompanied by endo-exo isomerization. Glycoside formation was postulated to occur from formation of a carbonium ion at C-1 of the sugar concurrent with formation of an orthoacid group. Carbonium ion formation at C-1 could occur as either (1) the initial step, Fig. 7, or (2) subsequent to a trans-orthoesterification step to form a 1-O-(1,1-dialkoxyethyl) group, Fig. 8. The alcohol would then react with the C-1 carbonium ion to form both β- and α-glycosides and the orthoacid group would form an ester and an alcohol.

In a further study of the mechanism of glycoside formation from acid-catalyzed reactions of glycose 1,2-(alkyl orthoacetates), Dykes (35) concluded that the mechanism proposed by Hultman is valid for reactions run in inert solvents and at various alcohol concentrations. Thus, the mechanisms proposed by Hultman should apply to reactions of the 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose intermediate formed in the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reactions.

REACTION MECHANISM

The reaction scheme shown in Fig. 9 represents what is believed to be the mechanism of glucoside formation in the reaction of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide. The rate-determining step of the reaction is heterolysis of the carbon-bromine bond, assisted by the mercuric cyanide, which results in the formation of an ion pair. The ion pair is either attacked by the cyclohexanol to give the β-glucoside or it dissociates to form a free carbonium ion. The degree of free carbonium ion formation is dependent on the alcohol concentration.

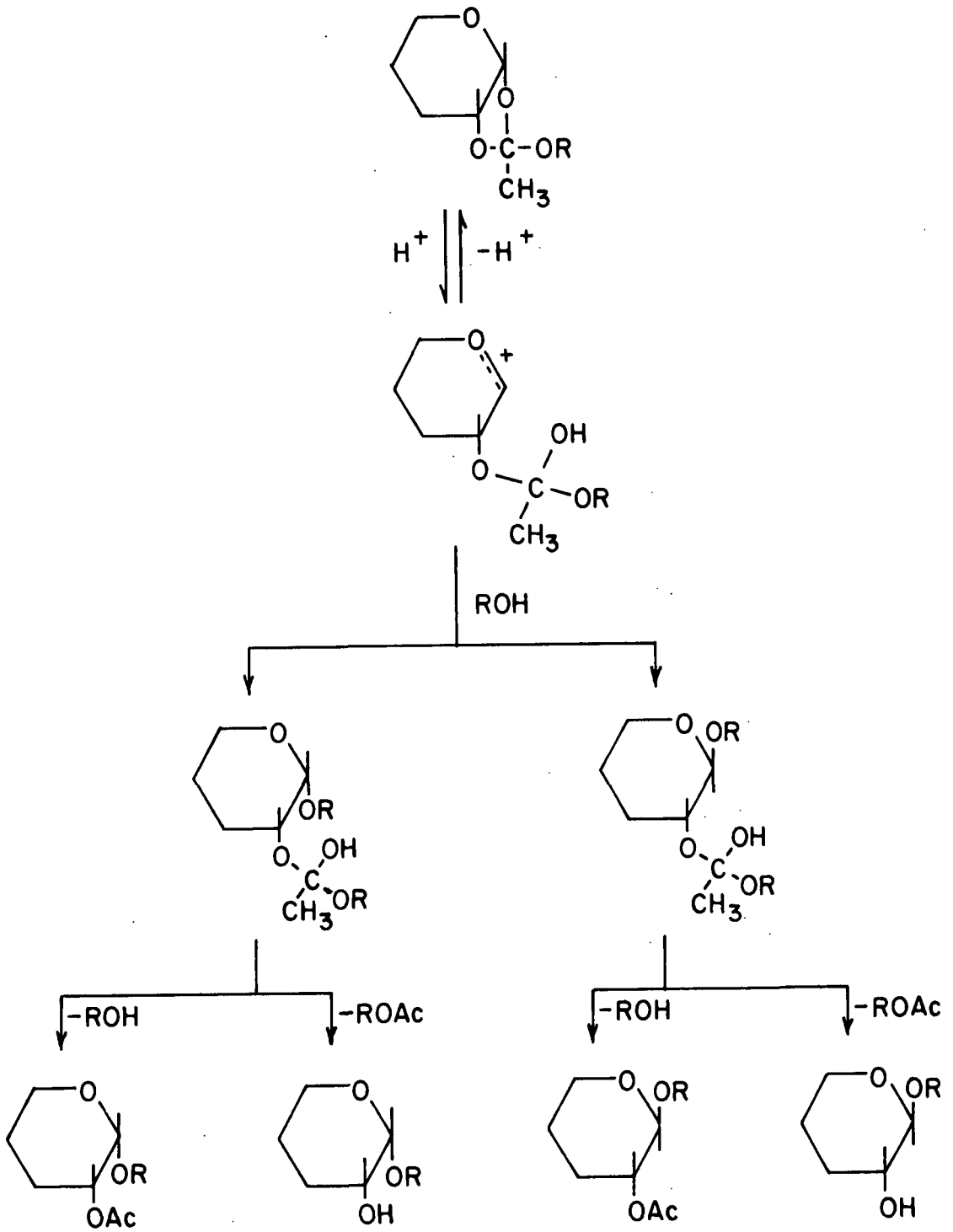


Figure 7. Glucoside Formation via Initial Bond Cleavage Between C-1 and O-1 as Proposed by Hultman (29). (The 3, 4, and 5 Substituents of the Pyranoid Rings are Not Shown.)

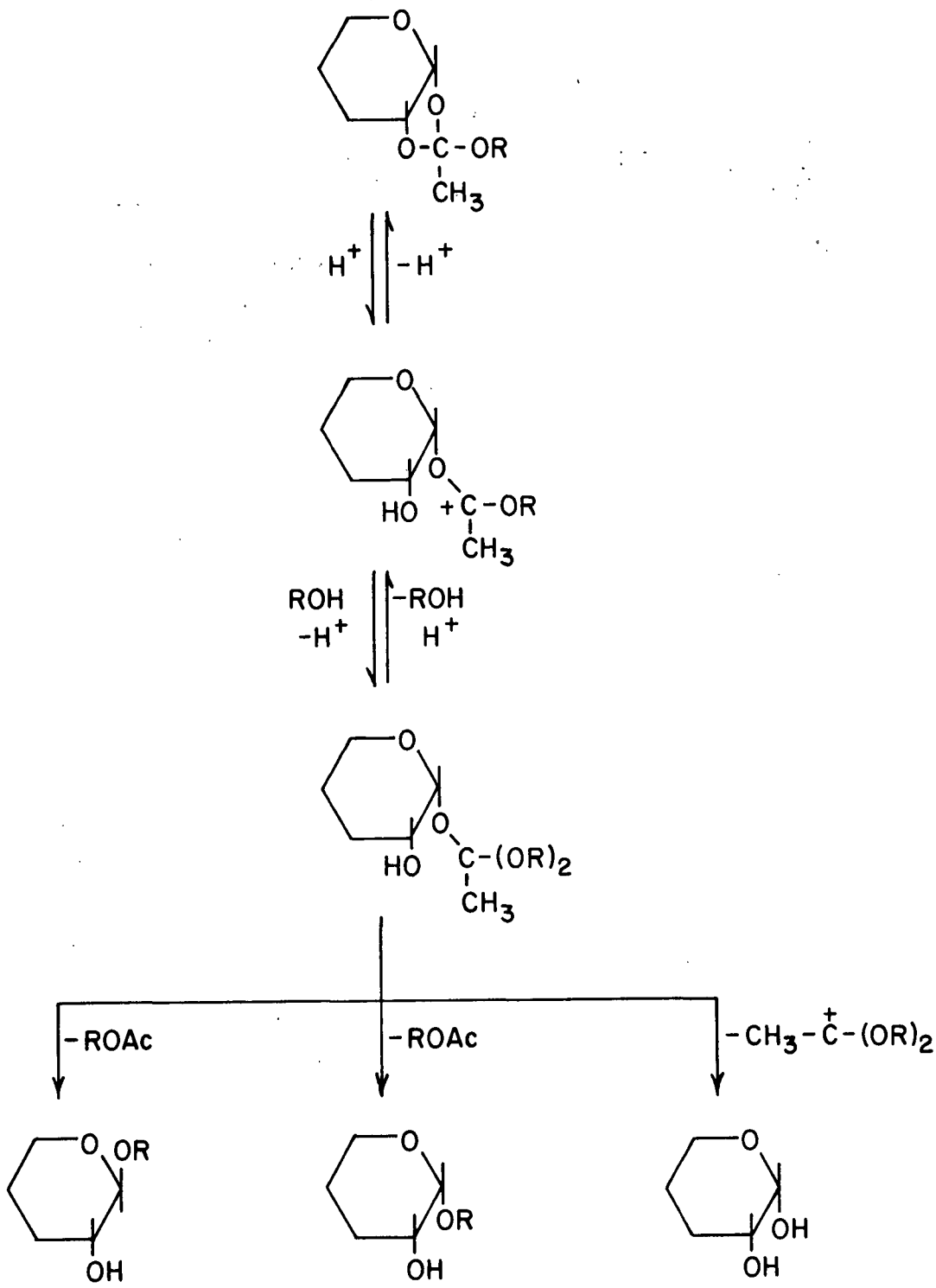


Figure 8. Glucoside Formation via Initial trans-Orthoesterification with Subsequent Bond Cleavage Between C-1 and O-1 as Proposed by Hultman (29). (The 3, 4, and 5 Substituents of the Pyranoid Rings are Not Shown.)

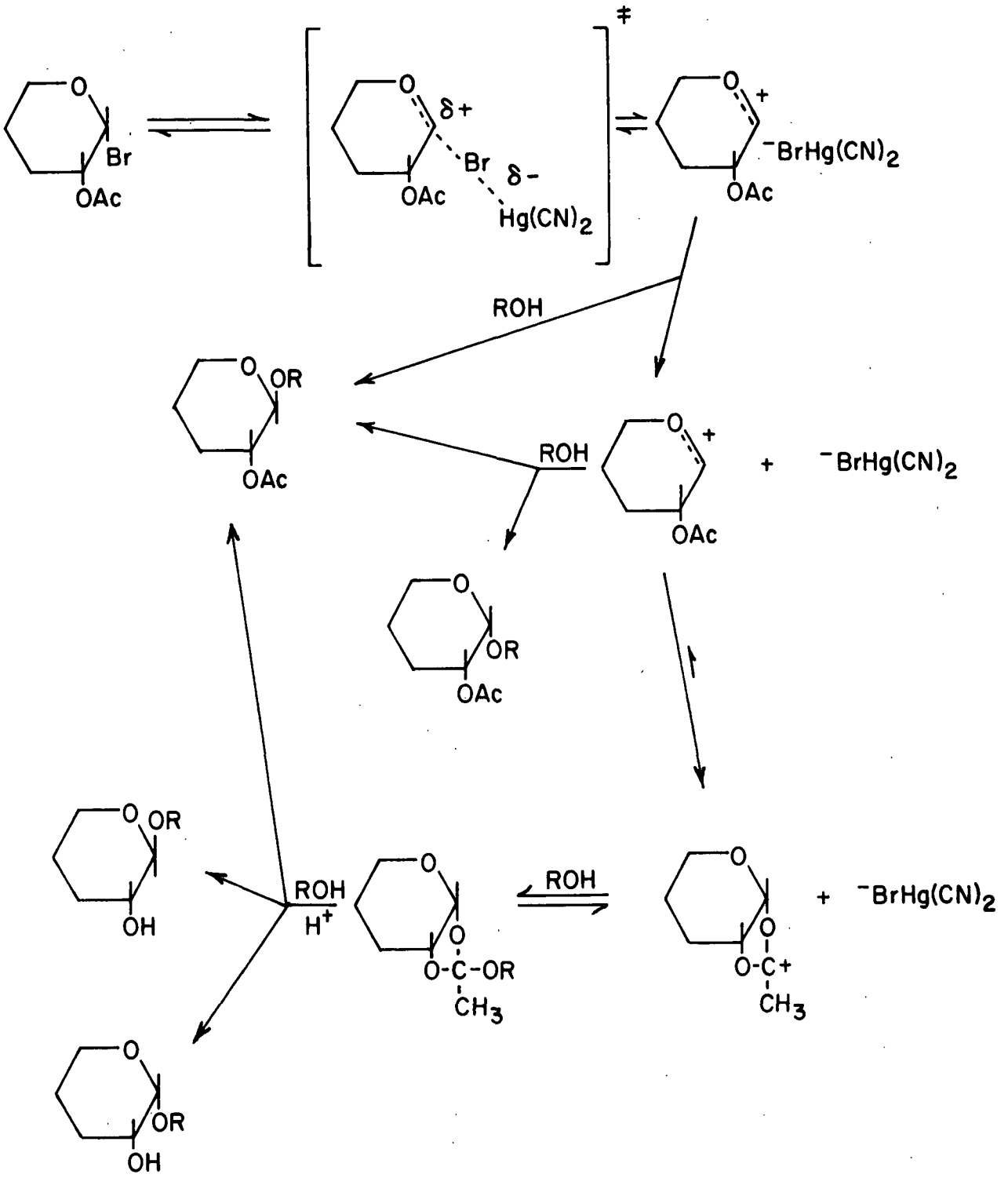


Figure 9. Proposed Mechanism for the Initial Reaction of 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide with Cyclohexanol in the Presence of Mercuric Cyanide; ‡ = Transition State. (The 3, 4, and 5 Substituents of the Pyranoid Rings are Not Shown.)

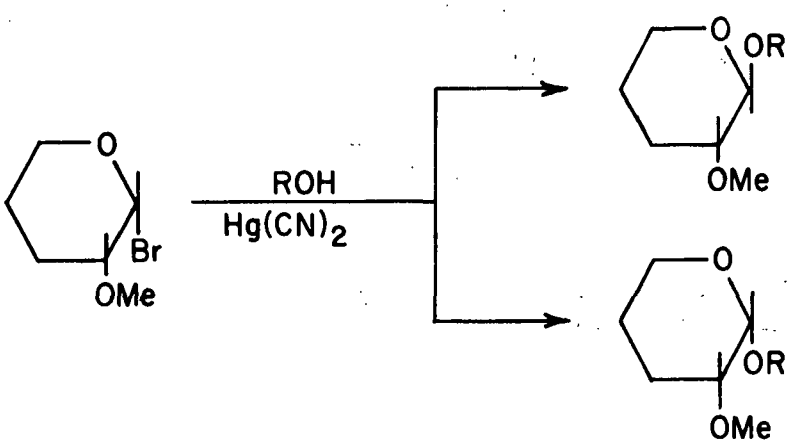
The free carbonium ion reacts either with cyclohexanol to give the α- and β-glucosides or with 2-O-acetyl carbonyl oxygen atom to form the 1,2-dioxolenium ion. Attack by cyclohexanol on the α-side of the free carbonium ion is the only significant pathway for formation of the 2-O-acetyl-α-glucoside.

Reaction of cyclohexanol with the 1,2-dioxolenium ion leads to the formation of an orthoester. During the initial portion of the reaction, the orthoester is relatively stable. However, as the reaction proceeds, species are formed in the system which are more effective catalysts for the reaction of the orthoester with the cyclohexanol. The species are believed to be HBr and/or HCN. Reaction of the orthoester with cyclohexanol results in the formation of small amounts of 2-hydroxyglucosides in addition to the 2-O-acetyl-β-glucoside.

2,3,4,6-TETRA-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE REACTION

GENERAL

The results and their mechanistic implications for the reaction of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide in 1:1 nitromethane-benzene are discussed below. This reaction was not as complex as that of the 2-O-acetyl analog because of the "nonparticipating" C-2 substituent. As shown in Equation (15), the reaction resulted in



(15)

the formation of cyclohexyl 2,3,4,6-tetra-O-methyl-α- and -β-D-glucopyranoside. Although this reaction was not as complex, the mechanism of this reaction was, in many ways, similar to that of the 2-O-acetyl analog.

POLARIMETRIC RATE DATA

Calculation of Reaction Rates from Polarimetry

The initial rates of the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reactions with cyclohexanol in the presence of mercuric cyanide were determined from the optical rotation-time data[1] and Equation (16)[2]:

$$H = H_o(\alpha_t - \alpha_\infty)(\alpha_o - \alpha_\infty)^{-1}, \qquad (16)$$

where H = the concentration of glucosyl bromide at time t

H_o = the initial concentration of glucosyl bromide

α_t = the optical rotation of the reaction at time t

α_o = the initial optical rotation of the reaction (determined by extrapolating the polarimetric data to time zero)

α_∞ = the optical rotation of the reaction at long times (equilibrium rotation)

Equation (16) was derived from Equation (17)[2] and is valid only if the ratio of anomers in the cyclohexyl glucosidic products is constant throughout the reaction. The product distribution data given in Appendix VI show that the ratio of anomeric products was time-independent for all the reaction temperatures and ratios of reactants employed.

$$H = H_o(\alpha_t - M)(\alpha_o - M)^{-1}, \qquad (17)$$

---

[1]The optical rotation-time data for 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reactions are in Appendix IV.

[2]The derivation of Equations (16) and (17) are given in Appendix V.

where $\underline{M} = \underline{\ell}((\underline{\ell} - \underline{n})[\alpha_{\underline{a}}] + \underline{n}[\alpha_{\underline{b}}])(M_{\underline{G}}H_{o}/1000)$

$\underline{\ell}$ = the solution path length of the plane polarized light (dm)

$\underline{n}$ = the mole fraction of β-anomer in the glucosidic product

$[\alpha_{\underline{a}}],[\alpha_{\underline{b}}]$ = the specific optical rotation of the α- and β-glucosides, respectively

$M_{\underline{G}}$ = the gram molecular weight of the glucosidic products

As with the previous glucosyl bromide, the initial rate, $(d\underline{H}/d\underline{t})_{\underline{t}=0}$, of a 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reaction was determined from the initial linear portion of the glucosyl bromide concentration versus time curve, e.g., Fig. 10. As before, the curve was used only to determine when the initial portion deviated from linearity and the initial slope was determined by the methods of least squares.

Rate Equation

The initial rates of reaction, obtained for a series of reactions in which the concentration of only one reactant at a time was varied significantly, are given in Table XII. By plotting log $(d\underline{H}/d\underline{t})_{\underline{t}=0}$ against log $[H]_{\underline{t}=0}$, log $[ROH]_{\underline{t}=0}$, and log $[Hg(CN)_2]_{\underline{t}=0}$, Fig. 11, according to the logarithmic form of the expression $d\underline{H}/d\underline{t} = -\underline{k}[H]^{\underline{a}}[ROH]^{\underline{b}}[Hg(CN)_2]^{\underline{c}}$, it was determined that the initial rate of the reaction is proportional to $[H]^{1.04}$ and $[Hg(CN)_2]^{1.04}$ but independent of the cyclohexanol concentration. Thus, the initial rate expression for the reaction of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide is given by Equation (8), which is the same as the initial rate expression for the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction.

$$(dH/dt)_{t=0} = -k[H][Hg(CN)_2] \qquad (8)$$

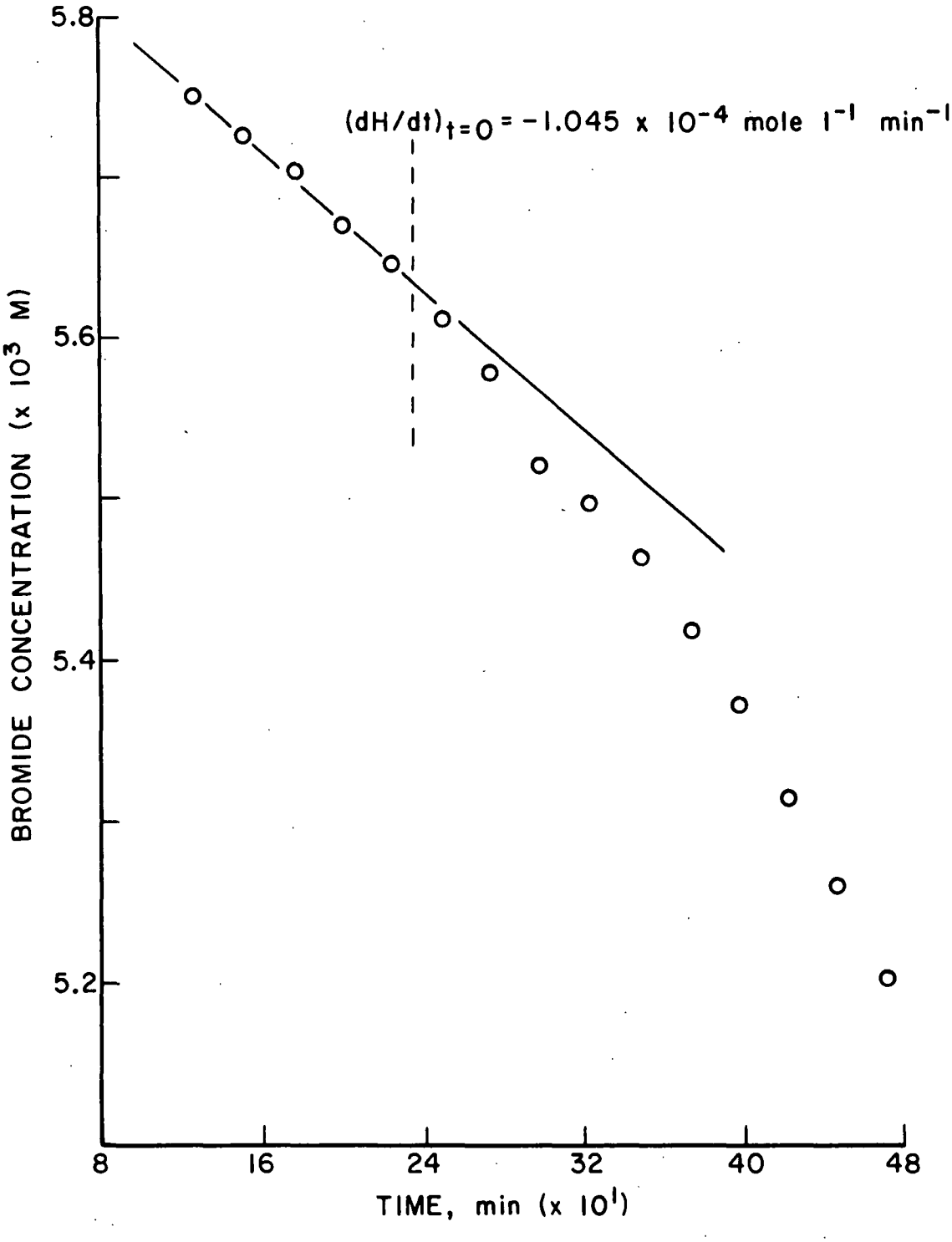


Figure 10. Plot of the Glucosyl Bromide Concentration Versus Time Determined from the Polarimetric Data of a Reaction of 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl Bromide with Cyclohexanol in the Presence of Mercuric Cyanide at 10°C

TABLE XII

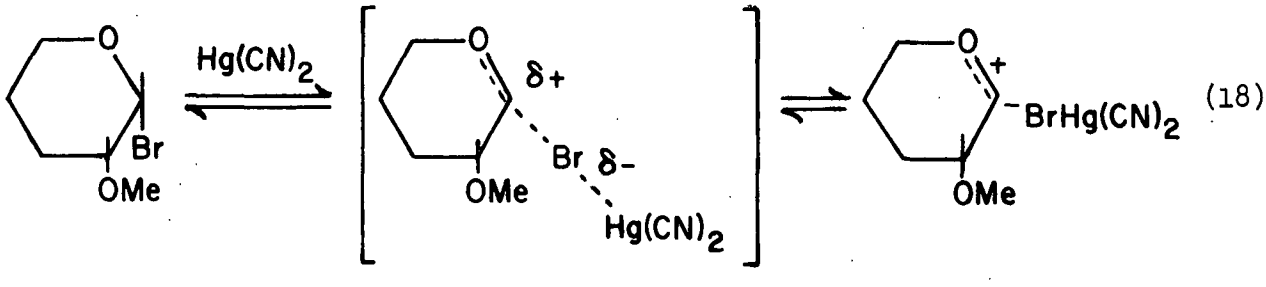
INITIAL RATES OF 2,3,4,6-TETRA-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE REACTIONS AT VARIOUS CYCLOHEXANOL, GLUCOSYL BROMIDE, AND MERCURIC CYANIDE CONCENTRATIONS (10°C)[a]

Reaction Number	Glucosyl Bromide (10^3M)	Cyclohexanol (10^2M)	$Hg(CN)_2$ (10^3M)	Initial Rate[b] (10^6 mole l^{-1} sec^{-1})
14	5.862	9.024	5.984	1.74
15	3.005	8.760	6.061	0.85
16	6.200	4.519	6.122	1.83
17	6.076	13.281	5.938	1.79
18	6.052	9.068	3.134	0.87
19	6.981	9.175	12.116	3.45

[a] Solvent, 1:1 nitromethane-benzene.

[b] Initial reaction rates calculated from optical rotation-time data and Equation (16). The polarimetric data are in Appendix IV.

The first-order kinetic dependence on the glucosyl bromide and the Lewis acid, mercuric cyanide, but not on the cyclohexanol, indicates that the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reactions occur by a Lewis acid-catalyzed unimolecular-type mechanism. The rate-determining step of the reaction is heterolysis of the carbon-bromine bond, assisted by the mercuric cyanide, as shown in Equation (18).



(18)

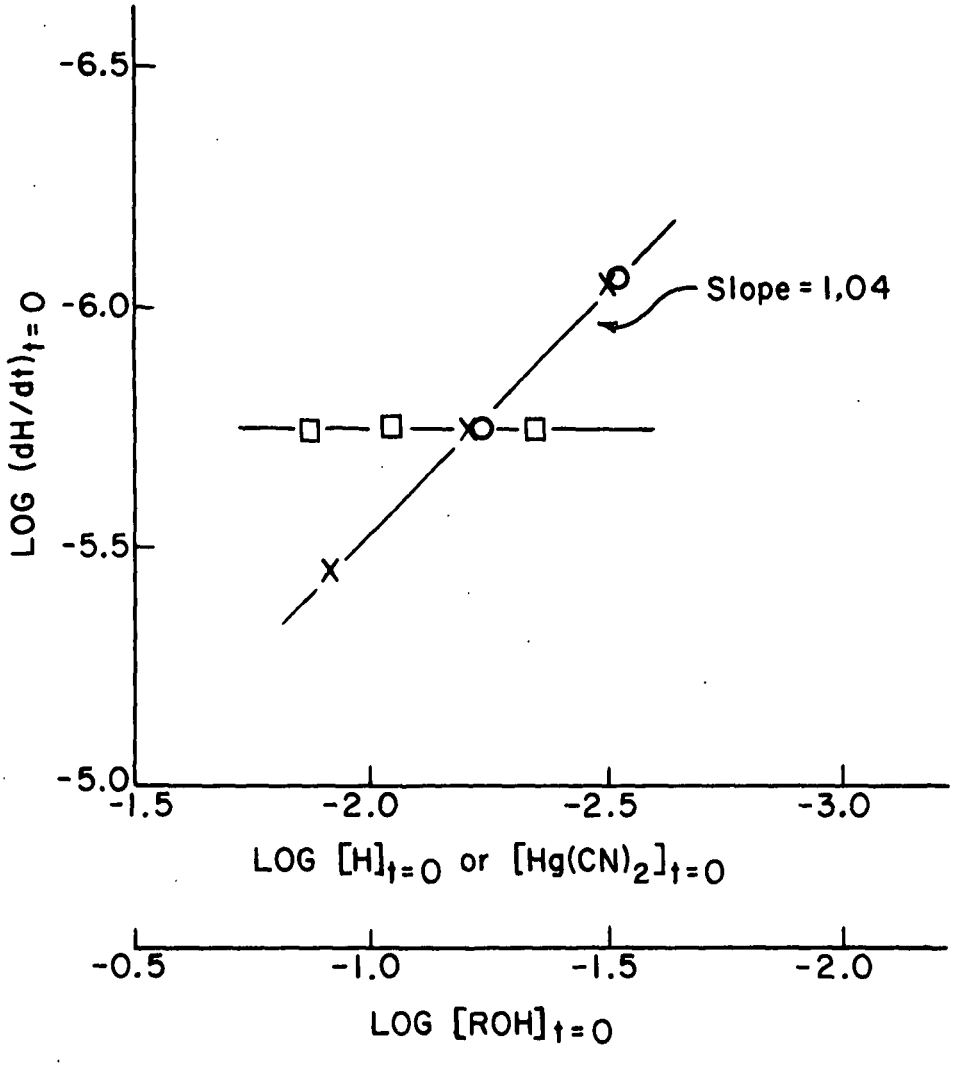


Figure 11. Plot of Log $(d\underline{H}/d\underline{t})_{\underline{t}=0}$ Versus Log $[H]_{\underline{t}=0}$, Log $[Hg(CN)_2]_{\underline{t}=0}$, and Log $[ROH]_{\underline{t}=0}$ for 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl Bromide Reactions at 10°C; x = $Hg(CN)_2$, o = RBr, □ ROH

Autocatalysis also occurred in the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reactions, e.g., see Fig. 10. As with the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reactions, the autocatalysis is believed to be due to the formation of other Lewis acids by reaction of the mercuric cyanide with the liberated bromide ion. Thus, the general rate equation for 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reactions is:

$$dH/dt = - \sum_{1}^{i} k_i[H][A_i]^{n_i} \qquad (10)$$

The autocatalysis is discussed in more detail in a later section.

GLUCOSIDE FORMATION

The fact that the initial rate of the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reaction is independent of the cyclohexanol concentration indicates that heterolysis of the carbon-bromine bond occurs prior to nucleophilic attack by the cyclohexanol. As with the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction, in order to determine whether shielding by the departing anion influences the stereochemistry of the products, the dependence of the product distribution on the cyclohexanol concentration was examined.

Table XIII gives the fraction of α-anomer formed in a series of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reactions in which only the cyclohexanol concentration was varied significantly[1]. As the cyclohexanol concentration was increased, the reactions became more selective for β-glucoside formation ($n_{-\alpha}$ decreased) which indicates that the departing anion partially shields the α-side, or that the ions exist as an ion pair. An increase in the cyclohexanol concentration results in an increase in the rate of nucleophilic attack (due to the availability of the alcohol) relative to the rate of dissociation of the ion pair. Thus, the importance of shielding by the departing anion increases, and the yield of β-glucoside increases at higher alcohol concentrations.

[1]It has been shown that the product distributions of the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reactions investigated were time-independent.

TABLE XIII

MOLE FRACTION OF α-ANOMER (n_{α}) IN THE GLUCOSIDIC PRODUCTS OF 2,3,4,6-TETRA-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE REACTIONS[a] AS A FUNCTION OF THE CYCLOHEXANOL CONCENTRATION

Glucosyl Bromide (10^3M)	Cyclohexanol (10^2M)	$Hg(CN)_2$ (10^3M)	Temp., °C	n_{α}[b]
6.671	4.639	5.921	10.3	0.27
5.862	9.024	5.984	10.2	0.23
6.076	13.281	5.938	10.0	0.18
6.331	1.766	6.028	20.5	0.39
7.134	9.519	6.019	20.2	0.26

[a] Solvent, 1:1 nitromethane-benzene.

[b] Analyses of samples containing known concentrations of α- and β-anomeric glucosides indicated that the mole fraction of α-anomer in the glucosidic product could be determined within ±2 mole%.

Since the ion pair must dissociate prior to attack by the cyclohexanol on the α-side of the carbonium ion, formation of cyclohexyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside shows that some of the glucoside formation occurred via the free carbonium ion. In addition to attack on the α-side, the free carbonium ion must have been attacked by the cyclohexanol on the β-side to yield β-glucoside. The ratio of the formation of β-glucoside via the free carbonium ion relative to that formed via the ion pair is not known. It is known, however, that the relative importance of glucoside formation via the free carbonium ion was dependent on the cyclohexanol concentration.

The dependence of the configuration of the products on the reaction temperature is given in Table XIV. The mole fraction of α-glucoside appears

to increase as the reaction temperature increases. These data indicate that an increase in the reaction temperature results in an increase in the rate of dissociation of the ion pair relative to the rate of nucleophilic attack by the cyclohexanol. This leads to an increase in the relative importance of glucoside formation via the free carbonium ion, and thus an increase in the yield of α-glucoside.

TABLE XIV

MOLE FRACTION OF α-ANOMER (n_{α}) IN THE GLUCOSIDIC PRODUCTS OF 2,3,4,6-TETRA-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE REACTIONS[a] AS A FUNCTION OF THE REACTION TEMPERATURE

Glucosyl Bromide (10^3M)	Cyclohexanol (10^2M)	$Hg(CN)_2$ (10^3M)	Temp., °C	n_{α}[b]
7.849	11.403	6.438	1.9	0.17
5.756	9.097	5.967	5.2	0.18
5.862	9.024	5.984	10.2	0.23
6.382	8.937	6.016	15.2	0.23
7.134	9.519	6.019	20.2	0.26

[a] Solvent, 1:1 nitromethane-benzene.

[b] Analyses of samples containing known concentrations of α- and β-anomeric glucosides indicated that the mole fraction of α-anomer in the glucosidic product could be determined within ±2 mole%.

REACTION MECHANISM

The reaction scheme shown in Fig. 12 represents what is believed to be the mechanism of glucoside formation in the reaction of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide. The rate determining step of the reaction is heterolysis of the

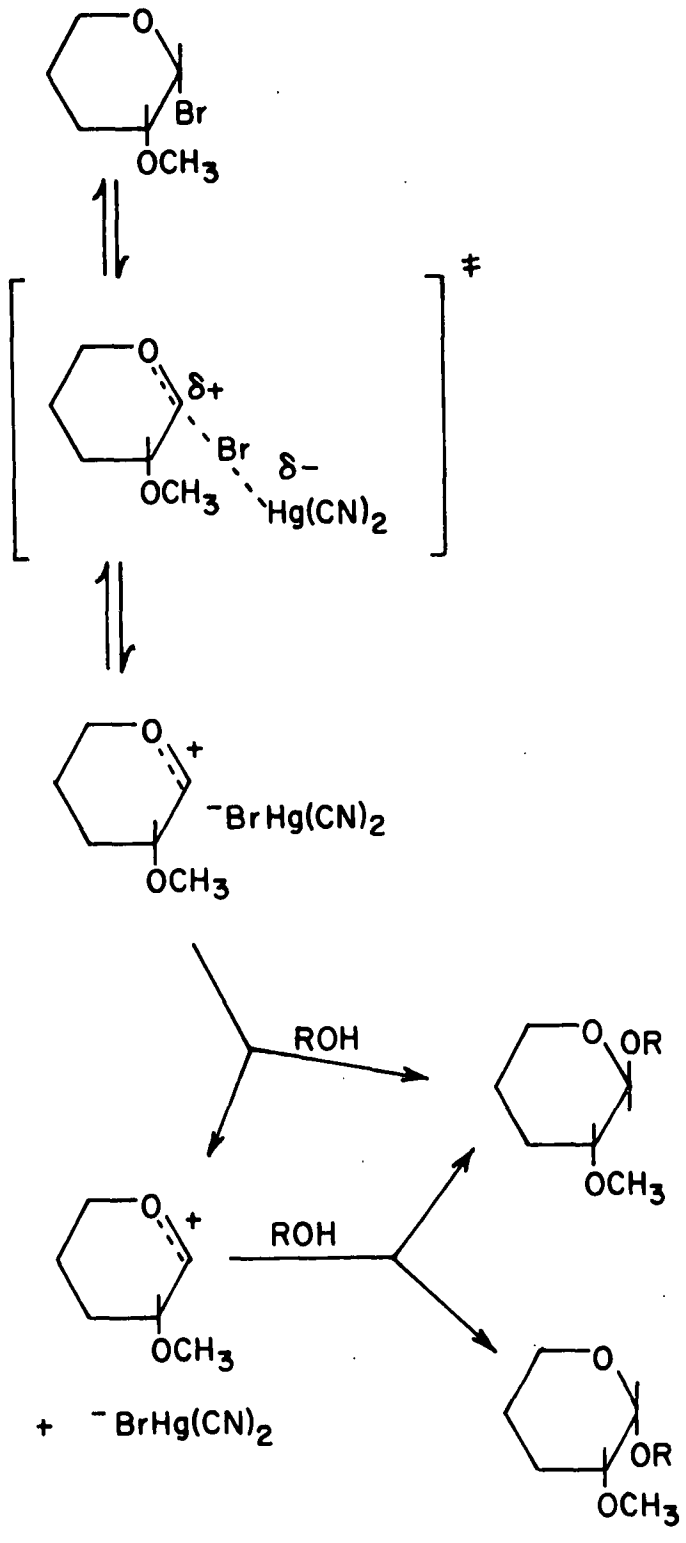


Figure 12. Mechanism Proposed for the Initial Reaction of 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl Bromide with Cyclohexanol in the Presence of Mercuric Cyanide; ‡ = Transition State. (The 3, 4, and 5 Substituents of the Pyranoid Rings are not Shown.)

carbon-bromine bond, assisted by the mercuric cyanide, resulting in the formation of an ion pair. The ion pair either reacts with cyclohexanol or dissociates to form a free carbonium ion. The relative importance of dissociation of the ion pair increases as the cyclohexanol concentration decreases and the temperature increases. Reaction of the free carbonium ion with cyclohexanol results in the formation of both the α- and β-glucoside.

THERMODYNAMIC FUNCTIONS OF ACTIVATION

CALCULATION OF THE INITIAL RATE CONSTANTS

The initial rate constants, k, for the reactions of both 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide and the 2-O-acetyl analog were obtained by dividing the initial rate of reaction[1] by the initial glucosyl bromide concentration and the mercuric cyanide concentration according to Equation (8). The initial rate constants, as a function of temperature, for the two glucosyl bromide reactions are given in Table XV. These data were used to determine the thermodynamic functions of activation.

COMPARISON OF THE THERMODYNAMIC FUNCTIONS OF ACTIVATION FOR THE TWO GLUCOSYL BROMIDE REACTIONS

The temperature dependence (Arrhenius Correlation) of the rate constants for the reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide and 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide in 1:1 nitromethane-benzene are shown in Fig. 13. The thermodynamic functions of activation, based on the slope and

---

[1] As discussed previously, the initial rates of reactions were calculated from the optical rotation-time data (given in Appendixes II and IV) and Equations (6) and (16).

intercept of the Arrhenius Correlation and calculated as described in Appendix VII, are given in Table XVI.

TABLE XV

INITIAL RATE CONSTANTS AS A FUNCTION OF TEMPERATURE FOR THE REACTIONS OF 3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE[a]

Reaction Number	C-2 Substituent	Temp., °C	$10^3 k$[b] (l mole^{-1} sec^{-1})
8	2-OAc	25	14.1
9, 10	2-OAc	20	8.84
11	2-OAc	15	5.81
1, 12	2-OAc	10	3.82
20, 21	2-OMe	20	87.2
22, 23	2-OMe	15	60.6
14, 15	2-OMe	10	46.7
24, 25	2-OMe	5	34.5
26, 27	2-OMe	2	23.6

[a] Reactions of glucosyl bromides with cyclohexanol in the presence of mercuric cyanide in 1:1 nitromethane-benzene.

[b] Initial rate constants were determined by dividing the initial rates by the glucosyl halide concentration and the mercuric cyanide concentration. The initial rate for each reaction is given along with the optical rotation-time in Appendixes II and IV.

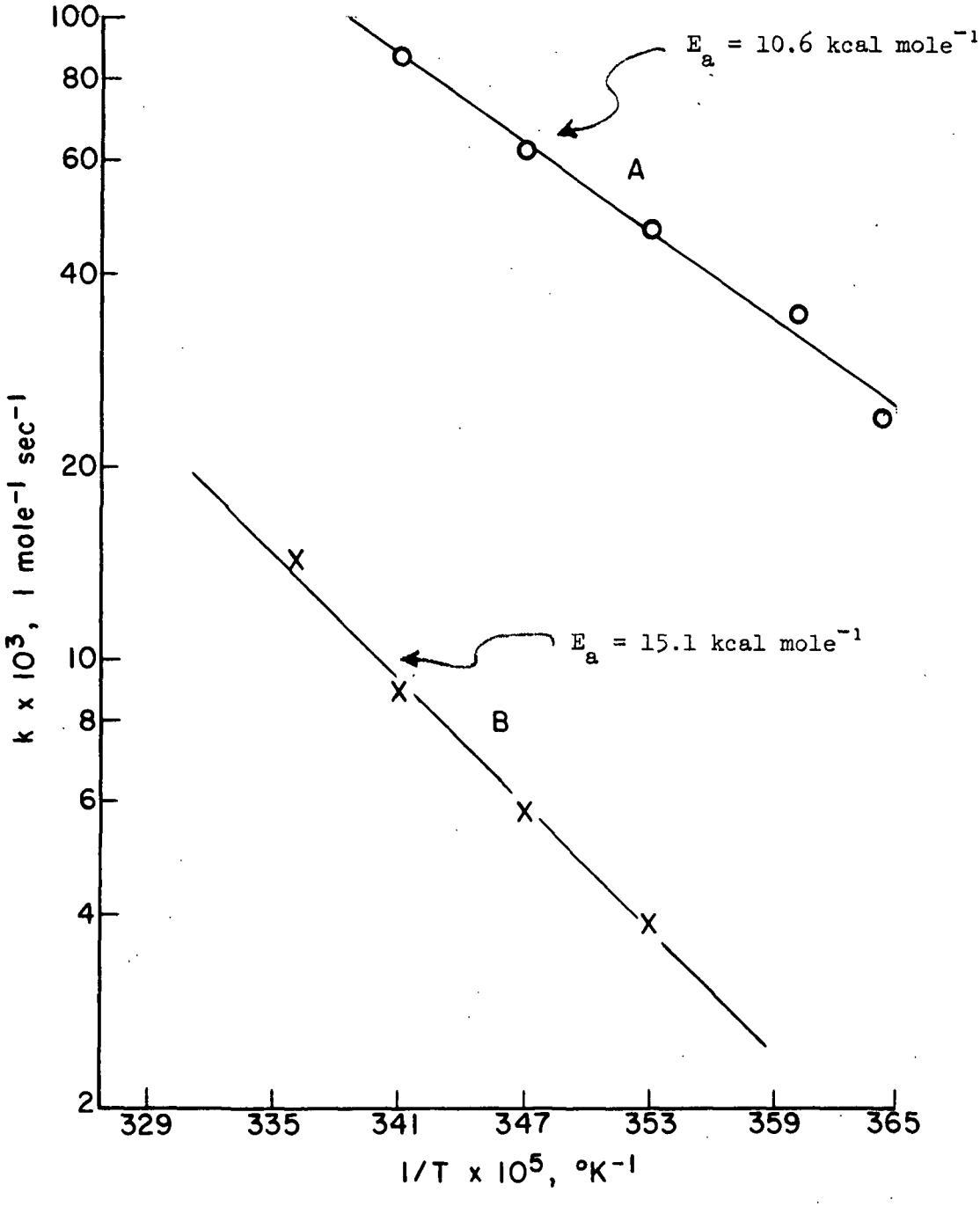


Figure 13. Arrhenius Correlation: Reactions of Glucosyl Bromides with Cyclohexanol in the Presence of Mercuric Cyanide in 1:1 Nitromethane-Benzene; A, 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl Bromide, B, 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide

TABLE XVI

THERMODYNAMIC FUNCTIONS OF ACTIVATION FOR REACTIONS OF THE GLUCOSYL BROMIDES WITH CYCLOHEXANOL IN THE PRESENCE OF MERCURIC CYANIDE (20°C)

Glucosyl Bromide	E_a, kcal mole^{-1}	$\Delta H^{\ddagger}$, kcal mole^{-1}	$\Delta S^{\ddagger}$, eu	$\Delta F^{\ddagger}$, kcal mole^{-1}
2-OAc[a]	15.1	14.5	-18.4	19.9
2-OMe[b]	10.6	10.0	-29.1	18.5

[a] 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide.

[b] 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl bromide.

The enthalpy of activation was 4.5 kcal greater for the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction than for the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reaction. This difference is believed to be caused by the greater electron withdrawing effect of the C-2 acetoxy substituent as compared to that of the C-2 methoxy substituent. The inductive substituent constant (σ_I) of a methoxy group is 0.25 whereas that of an acetoxy group is 0.39 (36). The greater electron withdrawing capacity of the C-2 acetoxy substituent causes the electron density of C-1 to be low relative to that of C-1 of the glucosyl bromide having a C-2 methoxy substituent. As a result of this lower electron density, more energy will be required for the heterolysis of the carbon-bromine bond, and this should be reflected in a higher enthalpy of activation.

The entropy of activation for both reactions was negative which indicates that the molecules in the transition state of each reaction were more constrained than were the reactants. However, the entropy of activation for the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction was more positive (11 eu) than that of the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl

bromide reaction. One possible explanation for this is that the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide molecule was more constrained in the initial state than the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide molecule. Thus, if the entropies of the transition states were about the same for the glucosyl bromides, the loss of freedom in going from the reactant to the transition state would have been less for the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide.

The 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide molecule could potentially be more constrained because of the repulsion between the carbonyl oxygen atom of the C-2 acetoxy group and the bromine atom at C-1 due to the polarization of the respective bonds. This repulsion would cause the carbonyl oxygen to be directed away from the C-1 bromine atom, and thus, restrict the freedom of the 2-O-acetyl substituent to rotate. This type of constraint probably does not exist in the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide molecule. In addition, this type of constraint would not be as important in the transition state because of the delocalization of the partial negative charge on the bromide atom by the mercuric cyanide. However, for both glycosyl bromides, the presence of mercuric cyanide in the transition state would be expected to hinder movement of the C-2 substituent.

AUTOCATALYSIS

GENERAL

In the case of both the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction and the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reaction, the rate of glucosyl bromide disappearance increased as the reaction proceeded. As discussed previously, it is believed that the autocatalysis was the result of the formation of other Lewis acids in the system by reaction of

mercuric cyanide with the bromide ion liberated as the glucosyl bromide reacted, e.g., Equations (19)-(24). Thus, some potential autocatalyzing species are HgCNBr, $HgBr_2$, HCN, HBr, and H^+.

$$RBr + Hg(CN)_2 \rightleftharpoons R^+ + Hg(CN)_2Br^- \quad (19)$$

$$R^+ + R'OH \longrightarrow ROR' + H^+ \quad (20)$$

$$Hg(CN)_2Br^- + H^+ \rightleftharpoons HgCNBr + HCN \quad (21)$$

$$Hg(CN)_2Br^- + H^+ \rightleftharpoons Hg(CN)_2 + HBr \quad (22)$$

$$RBr + HgCNBr \rightleftharpoons R^+ + HgCNBr_2^- \quad (23)$$

$$HgCNBr_2^- + H^+ \rightleftharpoons HgBr_2 + HCN \quad (24)$$

Table XVII gives the half-lives for reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide and the 2-O-acetyl analog with cyclohexanol in the presence of mercuric cyanide and mercuric bromide. For both of the glucosyl bromides, the data indicate that mercuric bromide is a more effective catalyst for the reactions than mercuric cyanide. Hence, formation of mercuric bromide in the reactions would cause the reactions to exhibit autocatalysis.

EFFECT OF THE CYCLOHEXANOL CONCENTRATION

The degree of autocatalysis exhibited by both of the glucosyl bromide reactions was dependent on the cyclohexanol concentration. Figures 14 and 15 are plots of the glucosyl bromide concentration versus time for the reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide and 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide, respectively, employing various alcohol concentrations. Note that the rates of glucosyl bromide disappearance appear to be dependent on the alcohol concentration, increasing with increasing alcohol concentration. However, it has been shown that the initial rate of both reactions is independent of the alcohol concentration. Thus, the alcohol concentration must affect the degree of autocatalysis exhibited by

the reaction and thereby give an "apparent" dependence of the reaction rates on the cyclohexanol concentration. It is possible that the cyclohexanol concentration influenced the degree of autocatalysis by influencing the equilibrium of Equations (20), (21), (22), and (24).

TABLE XVII

HALF-LIVES OF GLUCOSYL BROMIDE REACTIONS[a] CONDUCTED IN THE PRESENCE OF MERCURIC CYANIDE AND MERCURIC BROMIDE (10°C)

Reaction Number	Glucosyl Bromide (10^3M)		Cyclohexanol (10^2M)	$Hg(CN)_2$ (10^3M)	$HgBr_2$ (10^3M)	$t_{1/2}$[d], min
	2-OAc[b]	2-OMe[c]				
14	--	5.862	9.024	5.984	--	9.5
28	--	2.948	4.508	--	2.993	1.4
12	4.706	--	6.757	4.513	--	155
13	4.401	--	6.658	--	4.621	3.5

[a] Reactions of glucosyl bromides with cyclohexanol in 1:1 nitromethane-benzene.

[b] 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide.

[c] 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl bromide.

[d] Reaction half-life: time necessary for one-half of the glucosyl bromide to react. The half-life of each reaction is a function of the concentration of the reactants, particularly the mercuric cyanide or the mercuric bromide concentration. The half-lives were determined from the optical rotation-time data (Appendixes II and IV) and Equations (6) and (16).

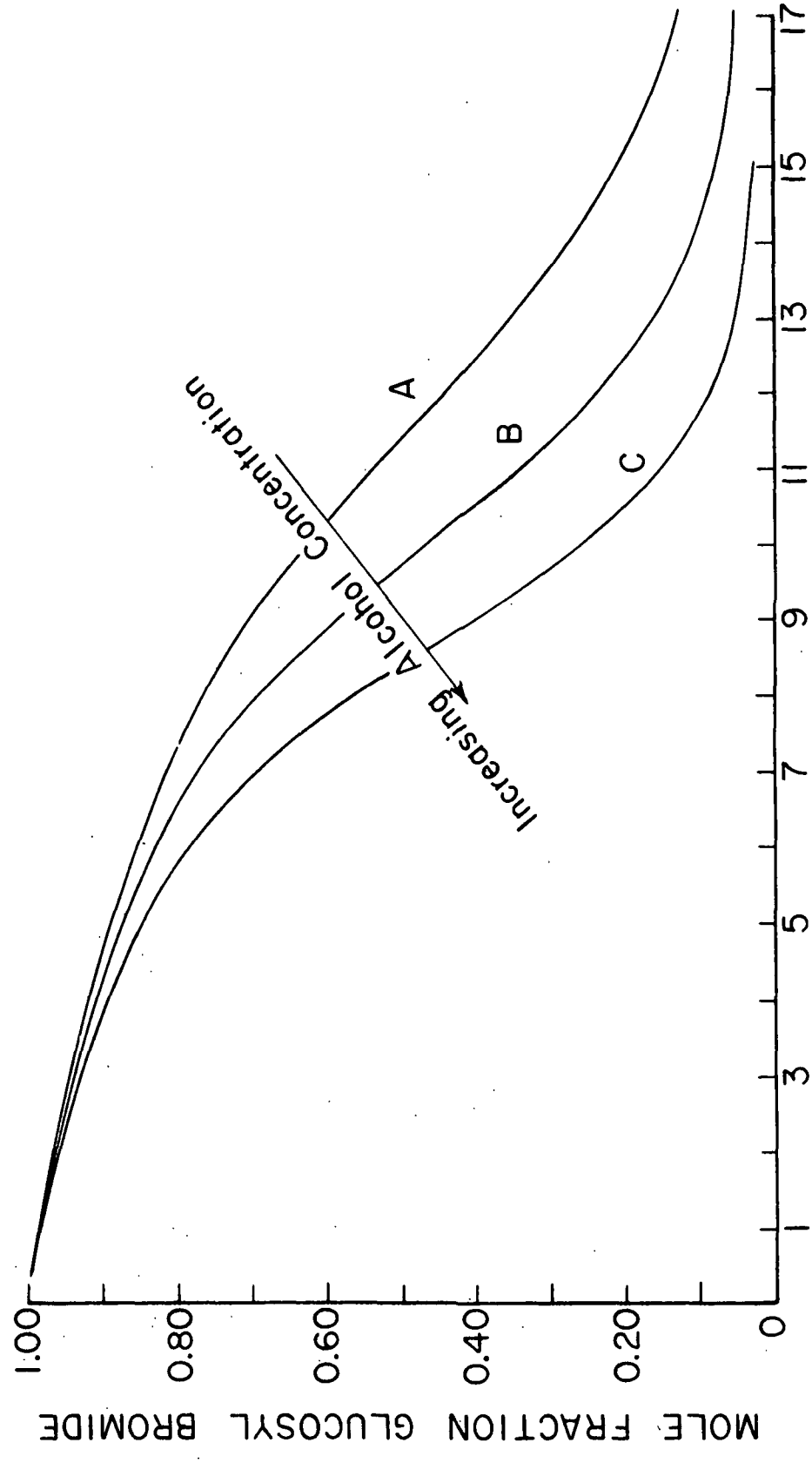


Figure 14. Mole Fraction of Glucosyl Bromide Remaining at Time t as a Function of the Cyclohexanol Concentration for the Reactions of 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl Bromide with Cyclohexanol in the Presence of Mercuric Cyanide; Concentration Ratio of ROH:RBr:$Hg(CN)_2$: A, 7.5:1:1; B, 15:1:1; C, 22.5:1:1

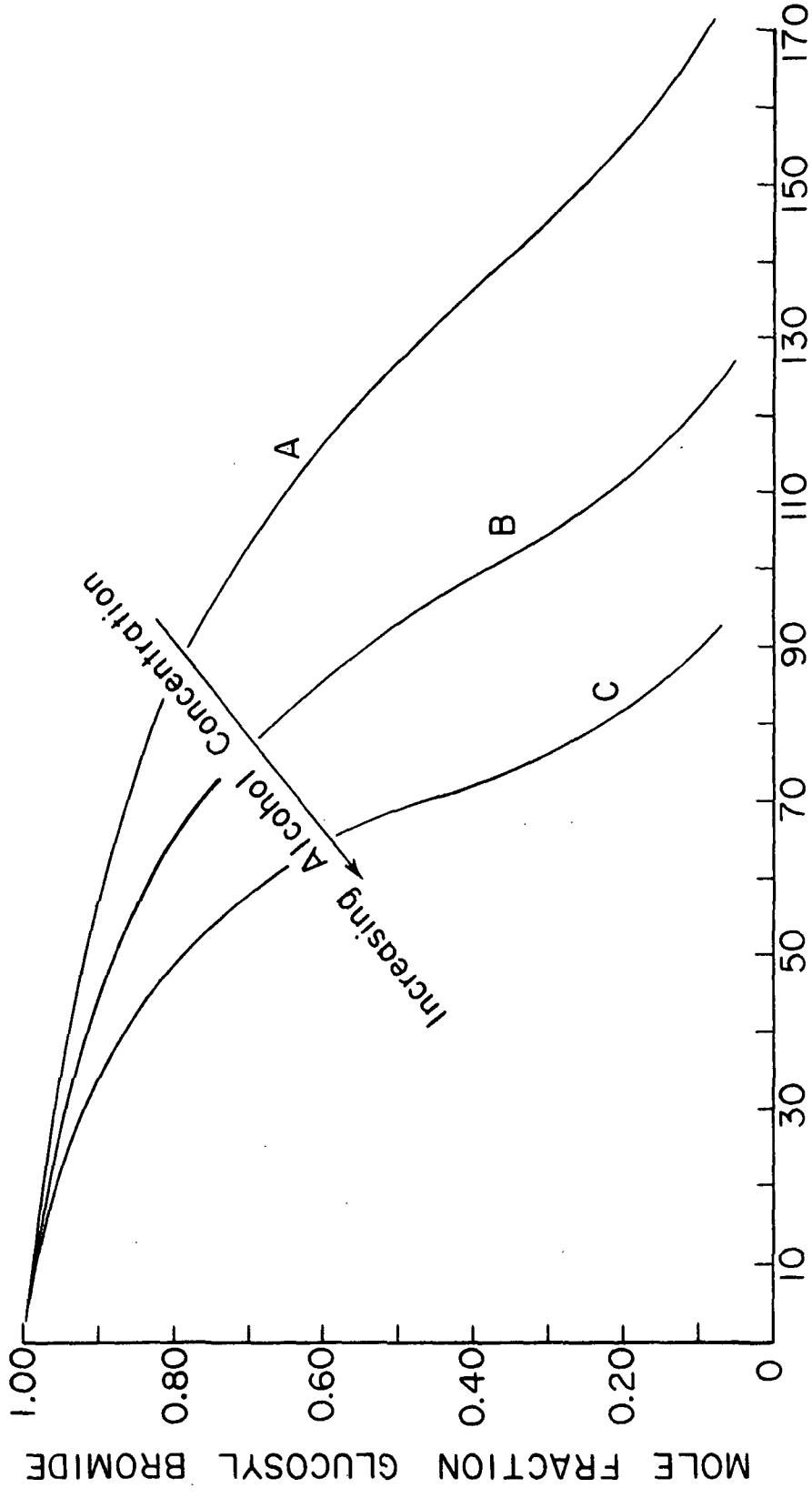


Figure 15. Mole Fraction of Glucosyl Bromide Remaining at Time $\underline{t}$ as a Function of the Cyclohexanol Concentration for the Reactions of 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide with Cyclohexanol in the Presence of Mercuric Cyanide; Concentration Ratio of ROH:RBr:$Hg(CN)_2$: A, 7.5:1:1; B, 15:1:1; C, 30:1:1

EFFECT OF THE 2-O-ACETYL SUBSTITUENT

The objective of this thesis was to determine the reason for the high degree of stereoselectivity observed in Koenigs-Knorr reactions involving 1,2-cis-glucopyranosyl halides having a 2-O-acetyl substituent as opposed to 1,2-cis-halides having "nonparticipating" C-2 substituents. Table XVIII gives the mole fraction of β-anomer in the glucosidic products for the reactions of 3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide in which various concentrations of cyclohexanol, glucosyl bromide, and mercuric cyanide were employed. As in the previous study (17), the data of Table XVIII indicate: (1) that the 2-O-acetyl bromide was much more selective toward formation of the β-anomer than the 2-O-methyl analog and (2) the steric course of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction was relatively unchanged by variation in the cyclohexanol concentration as compared to the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reaction.

Glucoside formation in the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction occurs as a result of attack by cyclohexanol at C-1 of either the ion pair or the free carbonium ion, or by reaction of the orthoester intermediate, formed via the 1,2-dioxolenium ion, with the cyclohexanol. As indicated by the results given in Table IX, the acid-catalyzed reaction of the orthoester with cyclohexanol selectively forms the 1,2-trans-2-O-acetyl glucoside. Thus, reaction of the 2-O-acetyl carbonyl oxygen with the C-1 of the free carbonium ion ultimately leads to selective formation of the 1,2-trans-2-O-acetyl glucoside.

TABLE XVIII

MOLE FRACTION OF β-ANOMER IN THE GLUCOSIDIC PRODUCTS OF THE 3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE REACTIONS (10°C)[a]

Conc. Ratio ROH:RBr:$Hg(CN)_2$[b]	Mole Fraction β-Anomer[c]	
	2-OAc[d]	2-OMe[e]
15:1:1	0.94	0.77
15:0:5:1	0.96	0.77
7.5:1:1	0.93	0.73
22.5:1:1	0.95	0.82
30:1:1	0.96	N.D.[f]
15:1:0.5	0.98	0.78
15:1:2	0.95	0.79

[a] Data taken from the final product distribution data given in Appendixes I and VI.

[b] Concentration ratio of cyclohexanol:glucosyl bromide: mercuric cyanide.

[c] Analyses of samples containing known concentrations of α- and β-anomeric glucosides indicated that the mole fraction of β-anomer in the glucosidic product could be determined within ±2 mole%.

[d] 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reactions.

[e] 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl bromide reactions.

[f] N.D. = not determined.

The data given in Table VII show that the initial mole ratio of ortho-ester to α-glucoside was about 5:1[1]. Thus, even assuming that formation of the 1,2-dioxolenium ion from the free carbonium ion is reversible, the ratio for the rate of reaction by the 2-O-acetyl carbonyl oxygen on the α-side of

[1] For the reaction employing a concentration ratio of alcohol:glucosyl bromide:mercuric cyanide equal to about 15:1:1.

the free carbonium ion to that by the cyclohexanol was at least 5:1. As the ion pair dissociates, the electron deficient anomeric carbon atom will attract any nucleophile in its environment. The carbonyl oxygen of the neighboring 2-O-acetyl substituent is in a position to donate electrons to the C-1 carbon resulting in 1,2-dioxolenium ion formation. Hence, the reason for the high rate of reaction by the C-2 acetoxy carbonyl oxygen as compared to that of the cyclohexanol on the α-side is believed to be the proximity of the 2-O-acetyl substituent to the C-1 relative to that of the alcohol. (Intramolecular reactions are generally faster than analogous intermolecular reactions.)

Thus, it is concluded that the high degree of stereoselectivity observed in the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction is due to (1) the high rate of reaction by the carbonyl oxygen on the α-side of the free carbonium ion leading to 1,2-dioxolenium ion formation as compared to that of the cyclohexanol which resulted in α-glucoside formation and (2) the stereoselectivity of the reaction of the orthoester, formed from the 1,2-dioxolenium ion, with the cyclohexanol to form 1,2-trans-O-acetyl glucoside.

These two factors are also the main reason that the product distribution of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction was relatively unchanged by variation in the alcohol concentration. As the alcohol concentration was decreased, a greater proportion of the ion pairs formed free carbonium ions prior to attack by the alcohol. In the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reaction, this resulted in an increase in the attack by the alcohol to the α-side of the C-1 and thus an increase in the yield of α-anomeric glucoside. With the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction, however, this resulted mainly in an increase in the attack by the carbonyl oxygen of the 2-O-acetyl group on the α-side of the C-1. Thus, the main change produced by the decrease in alcohol

concentration was that a greater percentage of the β-anomeric glucoside formation occurred via the orthoester intermediate.

CONCLUSIONS

The reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide and the 2-O-acetyl analog both exhibit first-order kinetic dependence on the glucosyl bromide and mercuric cyanide concentrations. Based on the observed autocatalysis, the reaction rates are shown to be dependent on other catalysts formed by the reaction of the liberated bromide ion with the mercuric cyanide. The rate-determining step of both glucosyl bromide reactions is the Lewis acid-catalyzed heterolysis of the carbon-bromine bond resulting in the formation of an ion pair.

Glucoside formation in the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reaction occurs as a result of attack by the cyclohexanol on either the ion pair to yield cyclohexyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside or the free carbonium ion, resulting from dissociation of the ion pair, to give cyclohexyl 2,3,4,6-tetra-O-methyl-α- and -β-D-glucopyranoside. The degree of free carbonium ion formation, and thus the yield of α-glucoside, is dependent on the alcohol concentration and the temperature.

Glucoside formation in the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction occurs as the result of: (1) attack by the cyclohexanol on the ion pair to yield cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside, (2) attack by the cyclohexanol on the free carbonium ion to form cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α- and -β-D-glucopyranoside, or (3) an acid-catalyzed reaction of cyclohexanol with 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose. The orthoester intermediate results

from attack by the C-2 acetoxy carbonyl oxygen on the α-side of the free carbonium ion. The degree of free carbonium ion formation, and thus the importance of the orthoester intermediate, is dependent on the alcohol concentration.

The acid-catalyzed reaction of the orthoester intermediate yields cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside and small amounts of cyclohexyl 3,4,6-tri-O-methyl-α- and -β-D-glucopyranosides. Hydrogen bromide and/or hydrogen cyanide are believed to be the dominant catalysts for this reaction.

Based on the product analysis of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction, it can be concluded that attack by the C-2 acetoxy carbonyl oxygen on the C-1 carbon of the carbonium ion is much more important than attack by the cyclohexanol on the α-side of the free carbonium ion. Since attack by the C-2 acetoxy carbonyl oxygen ultimately leads to the formation of mainly β-glucoside (via the orthoester intermediate) as does attack by the cyclohexanol on the ion pair, the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction is highly stereoselective.

Participation by the 2-O-acetyl substituent occurs after heterolysis of the carbon-bromine bond. Hence, the neighboring group exerts its influence on the product-determining step rather than on the rate-determining step of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction.

EXPERIMENTAL

GENERAL

Melting points were determined on a Thomas Hoover capillary apparatus which had been calibrated against known compounds.

Elemental analyses were performed by Chemalytics, Inc., 2330 S. Industrial Park Dr., Tempe, Arizona.

Optical rotations were measured on a Perkin-Elmer 141 MC polarimeter.

Nuclear magnetic resonance (NMR) spectra were determined with a Varian A-60A spectrometer at normal probe temperature using tetramethylsilane as an internal standard.

Thin-layer chromatography (TLC) plates were microscope slides coated with silica gel G. Once the TLC plates were spotted and developed, they were sprayed with methanolic sulfuric acid (20%, w/w) and heated for visualization of the spots.

Gas-liquid chromatography (GLC) analyses were conducted on a Varian Aerograph 1200-1 instrument equipped with a hydrogen flame-ionization detector and a Honeywell Electronic 16 recorder with a Disc integrator. All columns were made of stainless steel (0.125 inch, o.d.). The conditions used are as follows:

Conditions A: 5% SE-52 on 60/80 mesh Chromosorb W (5 ft); nitrogen, 14 ml/min; injector, 205°C; column, 160 → 220°C at 1°/min; detector, 265°C.

Conditions B: 5% SE-52 on 60/80 mesh Chromosorb W (10 ft); nitrogen, 8.2 ml/min; injector, 260°C; column, 200°C; detector, 265°C.

Conditions C: 30% Carbowax 20 M on 60/80 mesh Chromosorb W (3 ft); nitrogen, 60 ml/min; injector, 205°C; column, 160°C for 51 min, 160 → 220°C at 20°/min; detector, 265°C.

REAGENT PURIFICATION

Chloroform (37), cyclohexanol (1), methanol (38), and ethanol (29) were purified according to published procedures.

Thiophenol (1000 ml) was dried ($CaCl_2$) and fractionally distilled (40-cm Vigreux column) with the exclusion of moisture. The middle 500 ml of distillate was retained.

Benzene (1000 ml) was dried ($CaCl_2$), refluxed with lithium aluminum hydride, and fractionally distilled (40-cm Vigreux column) from lithium aluminum hydride with the exclusion of moisture. A portion (100 ml) of the retained distillate (middle 500 ml) was distilled off to azeotropically dry the benzene.

Nitromethane (2000 ml) was percolated through Drierite (8 mesh) twice. Following each percolation, the nitromethane was fractionally distilled (40-cm Vigreux column) with the exclusion of moisture. The middle half of the distillate was retained after each distillation. Finally, a portion (100 ml) of the retained distillate (500 ml) was distilled off to azeotropically dry the nitromethane.

Mercuric cyanide (100 g) was dissolved in hot absolute ethanol (800 ml), and a portion of the alcohol was distilled off to azeotropically dry the solution. The mercuric cyanide, which crystallized upon refrigeration, was dried *in vacuo* at 100°C for 24 hours and stored in a vacuum desiccator over phosphorus pentoxide.

PREPARATION OF COMPOUNDS AND PROOF OF STRUCTURE

2,3,4,6-TETRA-*O*-METHYL-D-GLUCOPYRANOSE

Methyl α-D-glucopyranoside (200 g) was acetylated with acetic anhydride and pyridine (39) to yield crystalline methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (329 g, 88%). Methylation of the acetylated glucoside (74.0 g) with dimethyl sulfate as described by Hultman (29,40) for the preparation of the methyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside yielded methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (44.3 g, 87%). The methylated glucoside was hydrolyzed by refluxing with 0.5*N* HCl (29). Crystallization of the crude product from petroleum ether (b.p. 60-110°C) yielded 2,3,4,6-tetra-*O*-methyl-D-glucopyranose (38.3 g, 92% based on the methylated glucoside): m.p. 84-93°C. Literature (41): m.p. 98°C (α-anomer).

1-*O*-ACETYL-2,3,4,6-TETRA-*O*-METHYL-D-GLUCOPYRANOSE

2,3,4,6-Tetra-*O*-methyl-D-glucopyranose (21.0 g) was acetylated with acetic anhydride-pyridine (126 ml; 1/2, v/v). After 2.5 hours the reaction mixture was poured into ice water, stirred for 0.5 hours, and extracted with chloroform (3 × 200 ml). The combined chloroform extracts were washed with 1*N* H_2SO_4, saturated sodium bicarbonate, and water; dried ($CaCl_2$); and concentrated *in vacuo* to yield 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-D-glucopyranose as a syrup (23.9 g, 91%); $[\alpha]_D$ + 101° (*c* 2.0, EtOH). Literature (40): $[\alpha]_D$ + 107° (*c* 1.9, EtOH).

2,3,4,6-TETRA-*O*-METHYL-α-D-GLUCOPYRANOSYL BROMIDE

1-*O*-Acetyl-2,3,4,6-tetra-*O*-methyl-D-glucopyranose (7.0 g) was stirred for 8 minutes with dichloromethane (220) saturated with HBr (15.5 g) and then poured into rapidly-stirred ice water. After 10 minutes, the solution was extracted with chloroform (3 × 100 ml). The combined chloroform extracts were washed successively with saturated sodium bicarbonate and water; dried ($CaCl_2$); and concentrated *in vacuo* to yield pure, as determined by TLC and NMR, 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl bromide as a syrup (6.1 g, 86%); $[\alpha]_D$ + 240° (*c* 1.1, $CHCl_3$), NMR δ($CDCl_3$) 6.58 ppm (1H, *d*, $J_{1,2}$ 3.5 Hz, H-1). The high specific optical rotation, the small $J_{1,2}$, and the low field position of H-1 are indicative of the α-anomer of the bromide.

The bromide was very unstable as a syrup and was stored in the refrigerator in anhydrous ethyl ether over Drierite to prevent its decomposition.

1,2-*O*-(1-*EXO*-ETHOXYETHYLIDENE)-3,4,6-TRI-*O*-METHYL-α-D-GLUCOPYRANOSE

3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-*exo*-ethoxyethylidene)-α-D-glucopyranose (50.0 g) (29,42) was methylated with dimethyl sulfate (29,42). 1,2-*O*-(1-*Exo*-ethoxyethylidene)-3,4,6-tri-*O*-methyl-α-D-glucopyranose was obtained as a syrup (37.4 g, 96%) and had $[\alpha]_D$ + 44° (*c* 1.4, $CHCl_3$). Literature (29): $[\alpha]_D$ + 45° (*c* 1.5, $CHCl_3$).

1-*O*- AND 2-*O*-ACETYL-3,4,6-TRI-*O*-METHYL-α-D-GLUCOPYRANOSE

1,2-*O*-(1-*Exo*-ethoxyethylidene)-3,4,6-tri-*O*-methyl-α-D-glucopyranose (37.0 g) was hydrolyzed with 0.1*N* H_2SO_4 (29,42). Crystallization of the crude product from isopropyl ether-petroleum ether (b.p. 30-60°C) (5/1, v/v) yielded 1-*O*- and 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranose (32.4 g, 96%);

m.p. 102-104°C, $[\alpha]_D$ + 111° (c 1.7, $CHCl_3$). Literature (29): m.p. 103.5-105°C, $[\alpha]_D$ + 116° (c 1.7, $CHCl_3$).

1,2-DI-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSE

A mixture of 1-O- and 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranose (28.0 g) was acetylated with pyridine and acetic anhydride as previously described for the preparation of 1-O-acetyl-2,3,4,6-tetra-O-methyl-D-glucopyranose. Crystallization of the crude product from isopropyl ether yielded 1,2-di-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranose (27.0 g, 84%); m.p. 63-64°C, $[\alpha]_D$ + 122° (c 1.8, $CHCl_3$). Literature (29): m.p. 64-65°C, $[\alpha]_D$ + 122° (c 1.9, $CHCl_3$).

3,4,6-TRI-O-METHYL-D-GLUCOPYRANOSE

A mixture of 1-O- and 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranose (32.4 g) was deacetylated with 0.025M methanolic sodium methoxide (200 ml). After 0.5 hour, the reaction mixture was concentrated in vacuo to a syrup. Crystallization of the crude product from isopropyl ether yielded 3,4,6-tri-O-methyl-D-glucopyranose (21.3 g, 78%); m.p. 68-92°C. Literature (43): m.p. 78-80°C (α-anomer), 97-98°C (β-anomer).

2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE

1,2-di-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranose (7.0 g) was treated with dichloroethane saturated with HBr as previously described for the preparation of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide. Pure 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide, as determined by NMR and TLC, was obtained as a syrup (6.7 g, 91%); $[\alpha]_D$ + 250° (c 0.9, $CHCl_3$), NMR δ($CHCl_3$) 6.65 (1H, d, $J_{1,2}$ 4.0 Hz, H-1), 4.65 (1H, m, $J_{1,2}$ 4.0 Hz, H-2), and

2.15 ppm (3H, s, OAc). The high specific optical rotation, the small $J_{1,2}$, and the low field position of H-1 are indicative of the α-anomer of the bromide.

The syrup was stored in the refrigerator in anhydrous ethyl ether over Drierite to prevent its decomposition.

3,4,6-TRI-O-ACETYL-1,2-O-(1-EXO-CYCLOHEXOXYETHYLIDENE)-α-D-GLUCOPYRANOSE

The title compound was prepared by reacting 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (120.0 g) (1) with cyclohexanol in the presence of tetraethyl ammonium bromide as described by Hultman (29,42) for the preparation of 3,4,6-tri-O-acetyl-1,2-O-(1-exo-ethoxyethylidene)-α-D-glucopyranose. Crystallization of the crude product from isopropyl ether containing a small amount of pyridine yielded 3,4,6-tri-O-acetyl-1,2-O-(1-exo-cyclohexoxyethylidene)-α-D-glucopyranose (60.0 g, 60%); m.p. 83-84.5°C, $[\alpha]_D$ + 26° (c 1.1, $CHCl_3$). Literature (44): m.p. 82-83°C, $[\alpha]_D$ + 28° ($CHCl_3$).

1,2-O-(1-EXO-CYCLOHEXOXYETHYLIDENE)-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSE

Methylation of 3,4,6-tri-O-acetyl-1,2-O-(1-exo-cyclohexoxyethylidene)-α-D-glucopyranose (20.0 g) with dimethyl sulfate as described by Hultman (29, 42) for the preparation of 1,2-O-(1-exo-ethoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose yielded 1,2-O-(1-exo-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose as a syrup (14.8 g, 93%). The syrup was purified by distillation under reduced pressure (0.05 mm Hg) through a 10-cm Vigreux column. The distillate had $[\alpha]_D$ + 37.4° (c 1.0, $CHCl_3$), NMR δ($CDCl_3$) 5.63 (1H, d, $J_{1,2}$ 5.2 Hz, H-1), 4.37 (1H, m, $J_{2,3}$ 3.1 Hz, H-2), 1.68 (3H, s, CH_3C), 3.41, 3.45, and 3.48 (3 × MeO), and 1.0-2.0 ppm (broad multiplet, H-cyclohexyl). (Found: C, 59.0; H, 8.6. $C_{17}H_{30}O_6$ requires C, 58.9; H, 8.7.)

n-BUTYL 2,3,4,6-TETRA-O-METHYL-β-D-GLUCOPYRANOSIDE

n-Butyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (57.4 g) (10) was methylated with dimethyl sulfate as described by Hultman (29,40) for the preparation of methyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside from the O-acetyl analog. n-Butyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside was obtained as a syrup (32.2 g, 78%). The syrup was distilled under reduced pressure (0.05 mm Hg) through a 10-cm Vigreux column. The distillate had $[\alpha]_D$ -29° (c 1.0, $CHCl_3$). (Found: C, 57.2; H, 9.5. $C_{17}H_{30}O_7$ requires C, 57.5; H, 9.7.)

CYCLOHEXYL 2,3,4,6-TETRA-O-METHYL-α-D-GLUCOPYRANOSIDE

Cyclohexyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside[1] (5.0 g) was deacetylated with 0.025M methanolic sodium methoxide. The resulting cyclohexyl α-D-glucopyranoside was methylated in dimethylformamide (50 ml) with methyl iodide (15 ml) and silver oxide (25 g — added portionwise) (45,46). After 2.0 hours, the reaction mixture was extracted with chloroform (3 × 200 ml). The combined chloroform extracts were washed with water (1 × 200 ml), dried ($CaCl_2$), and concentrated in vacuo. The cyclohexyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside obtained (3.4 g, 95%) was distilled under reduced pressure (0.05 mm Hg) through a 10-cm Vigreux column. The distillate had $[\alpha]_D$ + 148° (c 1.0, $CHCl_3$), NMR δ($CDCl_3$) 5.06 ppm (1H, d, $J_{1,2}$ 3.5 Hz, H-1). (Found: C, 60.6; H, 9.6. $C_{16}H_{30}O_6$ requires C, 60.3; H, 9.5.) The high specific optical rotation and small $J_{1,2}$ are indicative of the α-anomer of the cyclohexyl glucopyranoside.

[1]Obtained from L. R. Schroeder (1).

CYCLOHEXYL 2,3,4,6-TETRA-O-METHYL-β-D-GLUCOPYRANOSIDE

The title compound was prepared from 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (8.0 g) (10) using the same procedure as described for the preparation of cyclohexyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside from the O-acetyl analog. The cyclohexyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside was obtained as a syrup (5.4 g, 91%) and was purified by column chromatography employing silica gel (Sargent-Welch, 60-200 mesh) and chloroform-acetone (16/1, v/v). The fractions containing the desired product, as determined by GLC, were combined and concentrated in vacuo to a syrup. The syrup was distilled under reduced pressure (0.05 mm Hg) through a 10-cm Vigreux column. The distillate had $[\alpha]_D$ -27° (c 1.1, $CHCl_3$), NMR $\delta(CDCl_3)$ 4.34 ppm (1H, d, $J_{1,2}$ 7.0 Hz, H-1). (Found: C, 60.6; H, 9.5. $C_{16}H_{30}O_6$ requires C, 60.3; H, 9.5.) The low specific optical rotation and the $J_{1,2}$ are indicative of the β-anomer.

CYCLOHEXYL 2-O-ACETYL-3,4,6-TRI-O-METHYL-α- AND -β-D-GLUCOPYRANOSIDE

3,4,6-Tri-O-methyl-D-glucopyranose (26.4 g) was dissolved in cyclohexanol (130 ml) and acetyl chloride (5 ml). After 3 days of light heating, TLC (benzene-methanol, 5/1, v/v) indicated that glycosidation was complete. The reaction mixture was diluted with chloroform (400 ml), washed with water, dried ($CaCl_2$), and concentrated in vacuo to a syrup. The cyclohexyl 3,4,6-tri-O-methyl-D-glucopyranosides were acetylated with pyridine and acetic anhydride as described above for the preparation of 1-O-acetyl-2,3,4,6-tetra-O-methyl-D-glucopyranose. Cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α,β-D-glucopyranoside was obtained as a syrup (33.3 g, 81%).

Column chromatography, employing silica gel (Sargent-Welch, 60-200 mesh) and chloroform-ethyl acetate (20/1, v/v), was used to separate the anomers of cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranoside. The fractions containing the pure α-anomer, as determined by GLC, were combined and concentrated *in vacuo* to a syrup. The cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranoside was distilled under reduced pressure (0.05 mm Hg) through a 10-cm Vigreux column. The distillate had $[\alpha]_D$ + 162° (*c* 1.0, $CHCl_3$), NMR δ($CDCl_3$) 5.13 (1H, *d*, $J_{1,2}$ 3.8 Hz, H-1), 4.64 (1H, *m*, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 3.6 Hz, H-2), and 2.08 ppm (3H, *s*, OAc). (Found: C, 59.0; H, 8.9. $C_{17}H_{30}O_7$ requires C, 58.9; H, 8.7.) The high specific optical rotation and the small $J_{1,2}$ are indicative of the α-anomer.

The fractions containing the pure β-anomer, as determined by GLC, were combined and concentrated *in vacuo* to a syrup. Crystallization from petroleum ether (b.p. 30-60°C) yielded cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside; m.p. 58-59°C, $[\alpha]_D$ -25° (*c* 0.9, $CHCl_3$), NMR δ($CDCl_3$) 4.40 (1H, *d*, $J_{1,2}$ 8.0 Hz, H-1), and 2.08 ppm (3H, *s*, OAc). (Found: C, 59.1; H, 9.0. $C_{17}H_{30}O_7$ requires C, 58.9; H, 8.7.) The low specific optical rotation and $J_{1,2}$ are indicative of the β-anomer.

CYCLOHEXYL 3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSIDE

Cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranoside (1.0 g) was deacetylated with 0.025*M* methanolic sodium methoxide. After 3 hours, the solution was deionized (Amberlite MB-3) and concentrated *in vacuo* to yield cyclohexyl 3,4,6-tri-O-methyl-α-D-glucopyranoside (0.9 g, 100%); $[\alpha]_D$ + 144° (*c* 1.0, $CHCl_3$). Literature (47): $[\alpha]_D$ + 144° (*c* 1.4, $CHCl_3$).

CYCLOHEXYL 3,4,6-TRI-O-METHYL-β-D-GLUCOPYRANOSIDE

The title compound was obtained in pure form from Dykes (35).

PHENYL 2,3,4,6-TETRA-O-METHYL-1-THIO-β-D-GLUCOPYRANOSIDE

2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl bromide (4.9 g) in chloroform (100 ml) was treated with thiophenol (37.0 g) in 1M methanolic sodium methoxide (167.5 ml). The reaction, which was followed by TLC (ethyl acetate-benzene, 1/1, v/v), was complete within 1 minute. The reaction mixture was diluted with water (100 ml), extracted with chloroform (3 × 100 ml), washed with 10% aqueous sodium carbonate (3 × 150 ml) and water (150 ml), dried ($CaCl_2$), and concentrated *in vacuo* to a syrup (4.7 g, 87%). The syrup was purified by column chromatography, employing silica gel (Sargent-Welch, 60-200 mesh) and ethyl acetate-benzene (1/5, v/v). The fractions containing the desired product, as determined by TLC, were combined and concentrated *in vacuo* to a syrup. The syrup was distilled under reduced pressure (0.05 mm Hg) through a 10-cm Vigreux column. Crystallization from petroleum ether (b.p. 60-110°C) yielded phenyl 2,3,4,6-tetra-O-methyl-1-thio-β-D-glucopyranoside; m.p. 70.5-72°C, $[\alpha]_D$ -35.9° (*c* 1.0, $CHCl_3$), NMR δ($CDCl_3$) 4.50 (1H, *d*, $J_{1,2}$ 9.2 Hz, H-1) and 7.1-7.7 ppm (5H, *m*, SC_6H_5). (Found: C, 58.8; H, 7.3; S, 9.9. $C_{16}H_{24}O_5S$ requires C, 58.5; H, 7.3; S, 9.8.)

PHENYL 2-O-ACETYL-3,4,6-TRI-O-METHYL-1-THIO-β-D-GLUCOPYRANOSIDE

The title compound was prepared from 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide (7.0 g) using the same procedure as described for the preparation of phenyl 2,3,4,6-tetra-O-methyl-1-thio-β-D-glucopyranoside. Crude phenyl 2-O-acetyl-3,4,6-tri-O-methyl-1-thio-β-D-glucopyranoside was

obtained as a syrup (7.2 g, 95%) and was purified by column chromatography employing silica gel (Sargent-Welch, 60-200 mesh) and isopropyl ether. The fractions containing the desired product, as determined by TLC, were combined and concentrated *in vacuo* to a syrup. Crystallization from petroleum ether (b.p. 60-110°) yielded phenyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-1-thio-β-D-glucopyranoside; m.p. 68-69°C, $[\alpha]_D$ -0.8° (*c* 1.4, $CHCl_3$), NMR δ($CDCl_3$) *ca.* 4.58[1] (1H, *d*, $J_{1,2}$ *ca.* 10.2 Hz[1], H-1), *ca.* 4.83[1] (1H, H-2), 2.12 (3H, *s*, OAc), and 7.1-7.7 ppm (5H, *m*, SC_6H_5). (Found: C, 57.4; H, 6.6; S, 9.2. $C_{17}H_{24}O_6S$ requires C, 57.3; H, 6.8; S, 9.0.)

ETHYL 3,4,6-TRI-*O*-METHYL-2-*O*-PROPIONYL-β-D-GLUCOPYRANOSIDE

Ethyl 3,4,6-tri-*O*-methyl-β-D-glucopyranoside (2.0 g), prepared by Hultman (29), was propionylated with propionic anhydride-pyridine (12 ml; 1/2, v/v). After 24 hours, the mixture was poured into ice water and stirred for 0.5 hour. The product was then extracted with chloroform (3 × 75 ml). The combined chloroform extracts were washed with 1*N* sulfuric acid (1 × 100 ml), saturated sodium bicarbonate (1 × 100 ml), and water (1 × 50 ml), dried ($CaCl_2$), and concentrated *in vacuo* (2.1 g, 93%). The syrup was distilled under reduced pressure (0.05 mm Hg) through a Kontes short path distillation apparatus. Crystallization of the distillate yielded ethyl 3,4,6-tri-*O*-methyl-2-*O*-propionyl-β-D-glucopyranoside; m.p. 38-39°C, $[\alpha]_D$ -20.5° (*c* 1.0, $CHCl_3$). (Found: C, 54.9; H, 8.5. $C_{14}H_{26}O_7$ requires C, 54.6; H, 8.4.)

[1]Not a first-order spectrum.

2,3,4,6-TETRA-O-METHYL-1-O-PROPIONYL-D-GLUCOPYRANOSE

2,3,4,6-Tetra-O-methyl-D-glucopyranose (2.0 g) was treated with propionic anhydride-pyridine (12 ml; 1/2, v/v). After 12 hours, the reaction mixture was poured into ice water, stirred for 0.5 hour, and extracted with chloroform (3 × 20 ml). The combined chloroform extracts were washed with 1N H_2SO_4, saturated sodium bicarbonate, and water, dried ($CaCl_2$), and concentrated *in vacuo* to a syrup (2.3 g, 93%). The 2,3,4,6-tetra-O-methyl-1-O-propionyl-D-glucopyranose was distilled under reduced pressure (0.05 mm Hg) through a 10-cm Vigreux column. The syrup had an $[\alpha]_D$ + 74° (*c* 1.0, $CHCl_3$). (Found: C, 53.5; H, 8.4. $C_{13}H_{24}O_7$ requires C, 53.4; H, 8.4.)

REACTIONS CONDUCTED IN THE 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE STUDY

This section describes the procedures employed for conducting and analyzing four different types of reactions: (1) the reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol which were analyzed by both polarimetry and GLC (kinetic studies), (2) the reactions of the glucosyl bromide with cyclohexanol which were analyzed by GLC only, (3) the reactions of 1,2-O-(1-*exo*-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose with cyclohexanol which were analyzed by GLC, and (4) the reaction of the glucosyl bromide with ethanol which was analyzed by NMR. The procedures for conducting the reactions analyzed by GLC only included addition of Drierite and the internal standard during the initiation of the reactions. No Drierite was employed, and the internal standard was added after the samples were obtained in the reactions that were analyzed by both polarimetry and GLC. The reactions of the orthoester

with cyclohexanol are included in this section because they constitute part of the study of glucoside formation in the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction.

The procedures for conducting and analyzing the reaction of the glucosyl bromide with the ethanol are described in the sub-section Nuclear Magnetic Resonance Analysis.

PROCEDURES FOR INITIATING AND SAMPLING THE REACTIONS

Anhydrous conditions were imperative throughout the procedures given below because of the sensitivity of the glucosyl bromide and the orthoester to hydrolysis. All glassware used to conduct the reactions was dried at 180°C for 24 hours to remove the sorbed moisture. The glassware was then cooled in a vacuum desiccator over phosphorus pentoxide.

Mercuric cyanide was weighed into a 50-ml volumetric flask. Anhydrous nitromethane (35 ml) was pipeted into the volumetric flask, and the mercuric cyanide was dissolved by refluxing the nitromethane. Subsequently, nitromethane (10 ml) was distilled off to azeotropically dry the system. The flask was allowed to cool, and then weighed to determine the exact amount of nitromethane employed in the reaction. Depending on the reaction being conducted (see Table XIX) the appropriate compounds were weighed into the flask containing the nitromethane. The solvent transfer and weighing of compounds were conducted in a dry atmosphere to reduce the possibility of contamination by water.

Anhydrous benzene (35 ml) was pipeted into a second 50-ml volumetric flask. Benzene (10 ml) was distilled off to azeotropically dry the system. The flask was allowed to cool, and then it was weighed to determine the exact

amount of benzene employed in the reaction. The appropriate compounds (see Table XIX) were weighed into the flask containing benzene. As before, the solvent transfer and weighing of compounds were done in a dry atmosphere.

TABLE XIX

SOLUTION COMPOSITIONS FOR REACTIONS OF 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE AND 1,2-O-(1-EXO-CYCLOHEXOXYETHYLIDENE)-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSE WITH CYCLOHEXANOL IN THE PRESENCE OF MERCURIC CYANIDE

Reactions	Nitromethane	Benzene
Analyzed by Polarimetry and GLC		
Glucosyl bromide[a]	Mercuric cyanide Cyclohexanol	Glucosyl bromide
Analyzed by GLC Only		
Glucosyl bromide	Mercuric cyanide Cyclohexanol Internal standard[b] Drierite	Glucosyl bromide Drierite
Glucosyl bromide with addition of mercuric oxide	Mercuric cyanide Cyclohexanol Mercuric oxide Internal standard Drierite	Glucosyl bromide Drierite
Orthoester[c]	Mercuric cyanide Cyclohexanol Internal standard Drierite	Orthoester Drierite
Orthoester with addition of HBr	Mercuric cyanide Orthoester Internal standard Drierite	Cyclohexanol Hydrogen bromide Drierite

[a] 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide.

[b] Ethyl 3,4,6-tri-O-methyl-2-O-propionyl-β-D-glucopyranoside; employed as the internal standard for each reaction listed in this table.

[c] 1,2-O-(1-Exo-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose.

For the reactions in which Drierite was employed as a desiccant, the contents of the two volumetric flasks were stirred continuously for 4 hours to allow the Drierite time to further dry the solutions. The two volumetric flasks were placed in a water bath at the desired reaction temperature and allowed to thermally equilibrate for 30 minutes. A connecting tube was then placed between the two volumetric flasks, and the contents of the two flasks were mixed together. A sampling chamber (29) was attached to the flask containing the reaction mixture and the flask was returned to the water bath. Time zero for the reaction was taken to be the point at which the mixing of the nitromethane and benzene solutions began.

Use of the sampling chamber to take volumetric samples while maintaining anhydrous conditions is described elsewhere (29). Samples (5-ml aliquots), taken during the reactions of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide and from which the product distribution as a function of time was determined, were pipeted into a solution (0.38 ml) of methanolic sodium methoxide (0.5M)-thiophenol (10/1, v/v). The sodium methoxide-thiophenol quenched the reaction by converting the unreacted glucosyl bromide to phenyl 2-O-acetyl-3,4,6-tri-O-methyl-1-thio-β-D-glucopyranoside. Also, the basicity of the quenching system stabilized any 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose present in the sample. Samples taken of the final reaction mixture, obtained after a minimum of 10 hours reaction time, were pipeted into triethylamine-toluene (2.0 ml; 3/7, v/v) to stabilize any orthoester that might have been present. Samples taken of the reactions of 1,2-O-(1-exo-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose with cyclohexanol were also pipeted into triethylamine-toluene (2.0 ml; 3/7, v/v). All of the samples were sealed against moisture and stored in the refrigerator.

As discussed above, the internal standard, ethyl 3,4,6-tri-O-methyl-2-O-propionyl-β-D-glucopyranoside, was not added during the preparation of the reactions that were analyzed by polarimetry. Therefore, prior to the work-up of the samples from these reactions, the desired amount of a standard solution of internal standard in chloroform was pipeted into the samples.

POLARIMETRIC ANALYSIS

The constant temperature polarimetric system was of the same design as that used by Schroeder (1). The cell used was glass with a glass jacket forming an annulus for circulating water around the cell, was 1-dm long, and held about 5.0 ml of solution.

A sample of the reaction mixture was transferred to the cell at the desired reaction temperature. Readings were begun about one minute from time zero. The polarimetric data collected are given in Appendix II.

CARBOHYDRATE ANALYSIS

Product Identification

The reactant and carbohydrate products of reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide were identified and measured quantitatively by GLC. Prior to GLC analysis, some of the components were chemically modified to derivatives which could be analyzed under the GLC conditions employed. In addition to converting the unreacted glucosyl bromide to phenyl 2-O-acetyl-3,4,6-tri-O-methyl-1-thio-β-D-glucopyranoside, these chemical modifications included: (1) hydrolysis of the 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose intermediate to 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose, and (2) O-propionylation of the free hydroxyl groups on the carbohydrates. (The exact procedure is given under Quantitative Measurement Procedures.)

For the samples of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction which were quenched with sodium methoxide-thiophenol, two sets of GLC conditions were employed in the analysis. This was necessary because an extraneous compound, which originated from the sodium methoxide-thiophenol quenching system, had the same retention time as that of 1-O- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose when GLC Conditions A were employed. Under GLC Conditions B these two compounds could be separated. Hence, GLC Conditions A were used to identify and quantitatively measure 3,4,6-tri-O-methyl-D-glucopyranose, cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α- and -β-D-glucopyranoside, cyclohexyl 3,4,6-tri-O-methyl-α- and -β-D-glucopyranoside, and phenyl 2-O-acetyl-3,4,6-tri-O-methyl-1-thio-β-D-glucopyranoside, whereas, GLC Conditions B were used to identify and quantitatively measure 1-O- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose.

Only GLC Conditions A were employed for reaction samples which were quenched with triethylamine-toluene. This included the final samples taken of reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide and samples taken from reactions of 1,2-O-(1-exo-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose.

Chromatogram A (Fig. 16) illustrates the GLC analysis of a synthetic mixture of the possible constituents of a sample from a 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction. The identities of the peaks are as follows:

(1) ethyl 3,4,6-tri-O-methyl-2-O-propionyl-β-D-glucopyranoside (internal standard),

(2) 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose [as O-propionyl derivatives; these two compounds are the

hydrolysis products of 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose],

(3) 3,4,6-tri-O-methyl-D-glucopyranose (as 1,2-di-O-propionyl derivatives),

(4) cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranoside,

(5) cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside,

(6) cyclohexyl 3,4,6-tri-O-methyl-α-D-glucopyranoside (as 2-O-propionyl derivative),

(7) cyclohexyl 3,4,6-tri-O-methyl-β-D-glucopyranoside (as 2-O-propionyl derivatives), and

(8) phenyl 2-O-acetyl-3,4,6-tri-O-methyl-1-thio-β-D-glucopyranoside (derivative of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide).

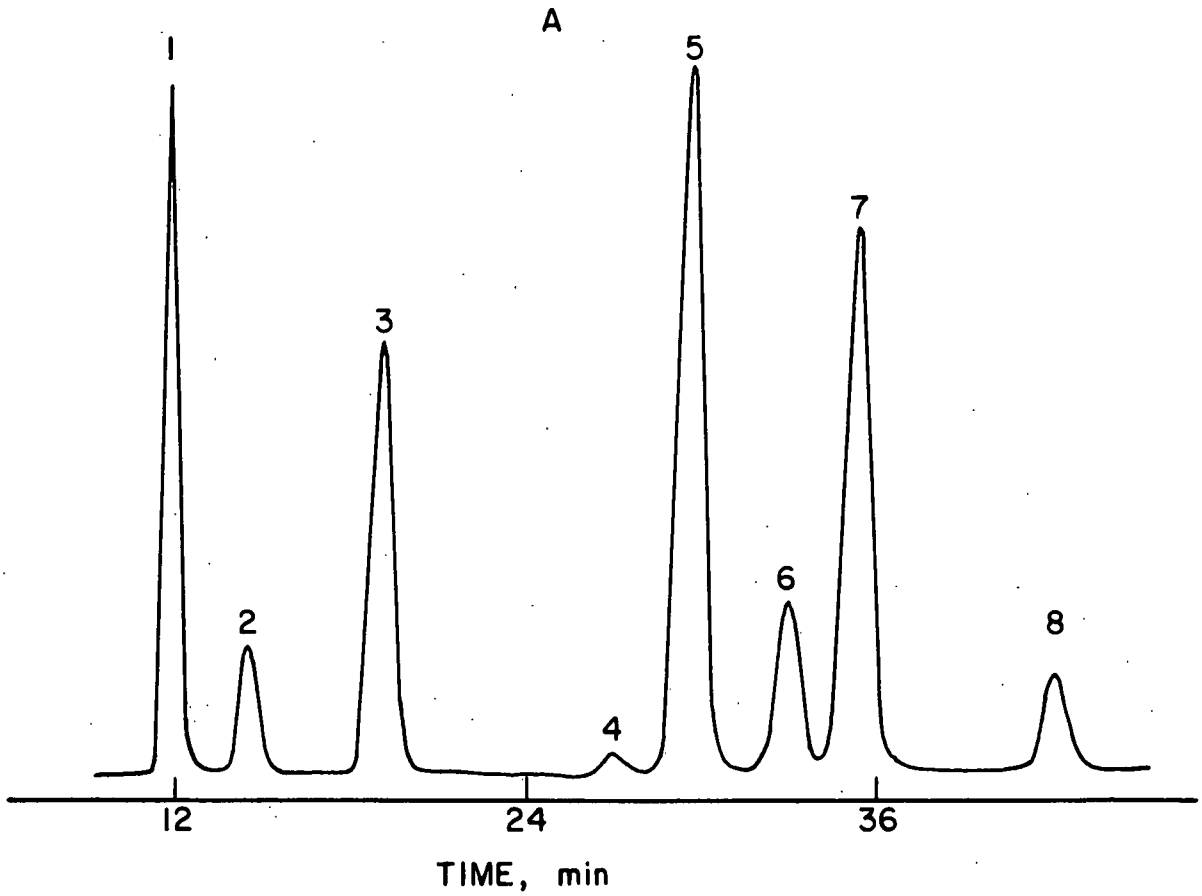


Figure 16. Chromatogram of a Synthetic Mixture of 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide Reaction Products; GLC Conditions A

Chromatograms B and C (Fig. 17) are reproductions of chromatograms obtained from analysis of a partially completed reaction of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide. Chromatogram C illustrates the GLC separation obtained with GLC Conditions B of the extraneous compound and 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose.

Chromatogram D (Fig. 18) illustrates the quantitative conversion of 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose to 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose by acid hydrolysis. No glucosidic product appeared in this chromatogram because the sample was taken very early in the reaction of 1,2-O-(1-exo-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose with cyclohexanol in the presence of mercuric cyanide. The very small peak for 3,4,6-tri-O-methyl-D-glucopyranose (3) illustrates that acid hydrolysis conditions were not drastic enough to cause a significant loss of O-acetyl groups from the initial orthoester hydrolysis products.

Quantitative Measurement Procedures

It has been mentioned previously that the 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose present in the reaction sample was hydrolyzed during the work-up to 1-O- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose. 1-O- and 2-O-Acetyl-3,4,6-tri-O-methyl-D-glucopyranose could, however, also have been formed during the reactions as a result of hydrolysis of either the glucosyl bromide or the orthoester due to the presence of water in the system. In order to quantitatively measure the 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose and the reaction hydrolysis product separately, each reaction sample was split into two aliquots and analyzed by Procedure A and Procedure B.

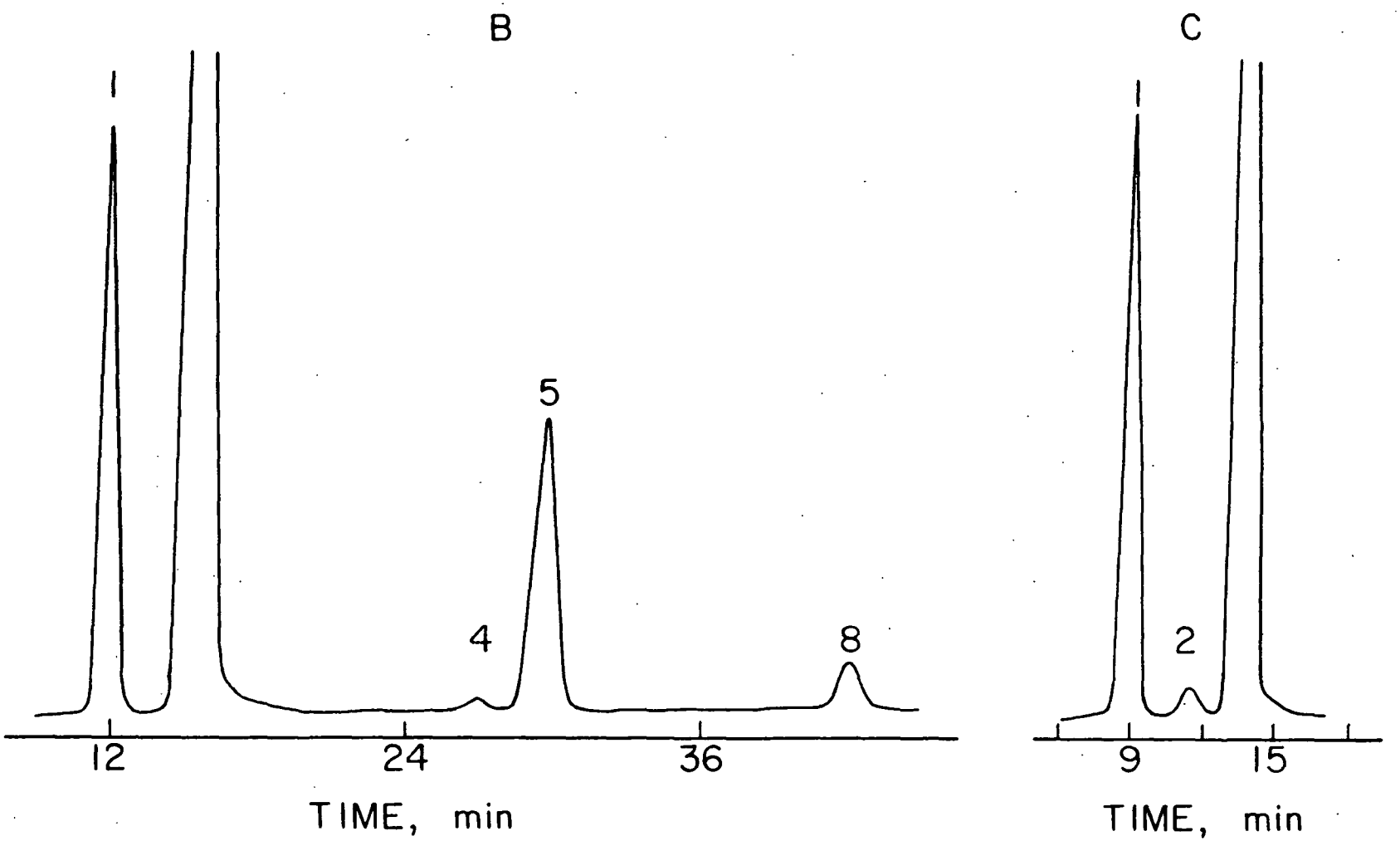


Figure 17. Chromatograms of a Partially Completed Reaction of 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl Bromide: B, GLC Conditions A; C, GLC Conditions B

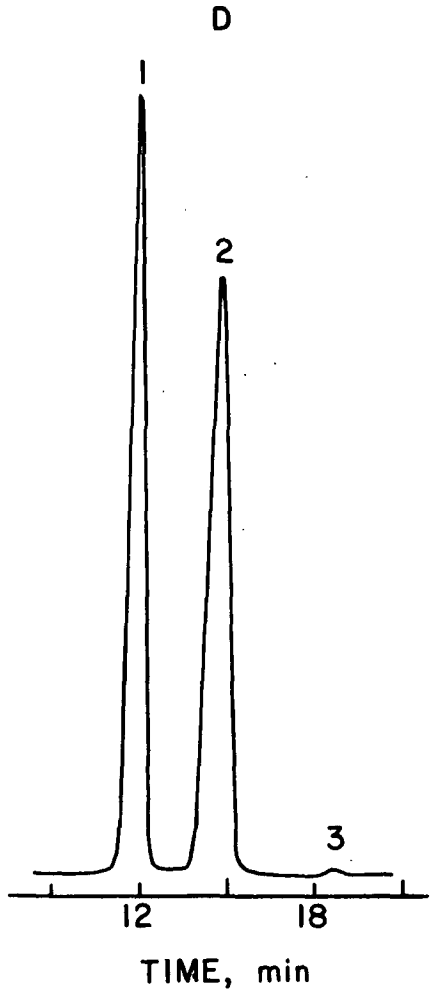


Figure 18. Chromatogram of a Hydrolysis of 1,2-O-(1-Exo-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose; GLC Conditions A

Procedure A consisted of hydrolysis of the 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose to 1-O- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose, and subsequent O-propionylation of the free hydroxyl groups of the carbohydrates. Using this procedure, both the orthoester intermediate and the reaction hydrolysis product were measured as the O-propionyl derivatives of 1-O- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose. Procedure B consisted of O-acetylation of the free hydroxyl groups of the carbohydrates, followed by hydrolysis of the 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose to 1-O- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose, and

subsequent O-propionylation of the free hydroxyl groups of the carbohydrates. Using this work-up procedure, only the orthoester intermediate unhydrolyzed at the time of sampling was measured as the O-propionyl derivatives of 1-O- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucopyranose. Hence, the amount of reaction hydrolysis product could be determined from the GLC analyses of the samples resulting from the two work-up procedures.

Procedure A

This procedure is a modification of that used by Hultman (29) for the ethanolysis of 1,2-O-(1-alkoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose. The aliquot (3.0 ml) of the sample was concentrated *in vacuo* to an oil. If the reaction was quenched with sodium methoxide-thiophenol, an aqueous solution (4 ml) of bromcresol purple[1] and sulfuric acid (1.0N, 4 drops) was added. If the reaction was quenched with triethylamine-toluene, only one drop of the 1.0 sulfuric acid was added along with the indicator. After 5 minutes, sodium hydroxide (0.01N) was added dropwise with swirling until the solution became purple. Buffer (0.4 ml, 0.1M K_2HPO_4 and 0.1M KH_2PO_4) was added, and the solution was concentrated *in vacuo*.

The sample was then treated with propionic anhydride-pyridine (ca. 2.0 ml; 1/1, v/v) and allowed to react (occasional swirling) at room temperature for a minimum of 24 hours. Water (15 ml) was added and after 15 minutes, the solution was extracted with chloroform (3 × 15 ml). The extracts were washed with 2N hydrochloric acid in a saturated sodium chloride solution (10 ml), with 1N sodium hydroxide in a 10% sodium chloride solution (10 ml), and water (10 ml). After each of the above washings, the aqueous phase was back-

[1]Twenty-five drops of bromcresol purple indicator (Harleco, 0.04% solution) were added to 100 ml of water.

extracted with a comparable volume of chloroform, and the chloroform solutions were combined before the next step.

The resultant chloroform solution was concentrated *in vacuo* to an oil. If any odor of propionic acid was detected, water was added to the sample, and the solution was reconcentrated to remove the residual propionic acid. The sample was dissolved in chloroform and analyzed by GLC using Conditions A and Conditions B as previously described under Product Identification. The response factors and their use in quantitative GLC are given in Appendix VIII.

Procedure B

The aliquot (2.0 ml) of the sample was concentrated *in vacuo* to an oil and allowed to react with acetic anhydride-pyridine (*ca.* 2.0 ml; 1/2, v/v) for a minumum of 24 hours. Water (15 ml) was added, and after 15 minutes the solution was extracted with chloroform (3 × 20 ml). The combined chloroform extracts were concentrated *in vacuo* to *ca.* 2.0 ml. Hydrochloric acid (1.0N, 15 ml) was added, the resultant mixture was shaken for 5 minutes and then extracted with chloroform (3 × 15 ml). The extracts were washed with 1N sodium hydroxide in 10% sodium chloride solution (5 ml) and water (5 ml). After each wash the aqueous phase was back-extracted with chloroform (10 ml) and the chloroform solutions were combined before the next step.

The resultant chloroform solution was concentrated *in vacuo* to an oil and treated with propionic anhydride-pyridine (*ca.* 2.0 ml; 1/2, v/v). The work-up procedure for the propionylation was the same as that given for Procedure A. On completion of the work-up, the concentrated sample was dissolved in chloroform and analyzed by GLC using Conditions B.

NUCLEAR MAGNETIC RESONANCE ANALYSIS

As discussed previously, the reaction of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with ethanol in the presence of mercuric cyanide in 1:1 nitromethane-benzene was analyzed by NMR to obtain direct evidence for the formation of the orthoester intermediate during the reaction of the glucosyl bromide. The broad cyclohexyl multiplet would partially mask the orthoacetyl methyl singlet of 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose. Therefore, ethanol was used in place of cyclohexanol in the reaction analyzed by NMR. Also, the concentration levels employed were too low to allow for direct NMR analysis of the reaction. Hence, it was necessary to conduct a large-scale reaction of the glucosyl bromide with ethanol, quench the reaction as it neared completion, concentrate the reaction mixture, and then analyze it in total by NMR. The procedure was as follows.

Anhydrous nitromethane (25 ml) was pipeted into a 50-ml volumetric flask containing mercuric cyanide (0.3054 g). The mixture was refluxed to dissolve the mercuric cyanide. The solution was allowed to cool, and ethanol (0.8062 g) was weighed into it. The solution was transferred into a 250-ml volumetric flask, and additional anhydrous nitromethane (75 ml) was pipeted into the flask.

Anhydrous benzene (25 ml) was pipeted into a second 50-ml volumetric flask. 2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide (0.3332 g) was weighed into the flask. The resultant solution was transferred to a second 250-ml volumetric flask, and additional anhydrous benzene (75 ml) was pipeted into the flask.

The above operations were conducted in a dry atmosphere to reduce the possibility of contamination by water.

The contents of the two flasks were thermostated at 10.0°C in a bath for one hour. The nitromethane solution was added to the benzene solution, mixed thoroughly, and stored in the 10.0° bath. Time zero was taken to be the point at which one-half of the nitromethane solution was added. A sample of the reaction mixture was transferred to a water-jacketed polarimeter cell at 10.0°C.

When the optical rotation of the reaction approached a constant value (ca. 90 min), the reaction was quenched with methanolic sodium methoxide (0.5M)-thiophenol (ca. 10 ml; 10/1, v/v), concentrated in vacuo to about 10 ml, filtered, washed with 1N sodium hydroxide (2 × 10 ml) and water (10 ml), and dried ($CaCl_2$). After addition of pyridine (ca. 2 ml) the sample was concentrated in vacuo to dryness. The sample was dissolved in $CDCl_3$ (ca. 0.4 ml) and analyzed by NMR.

REACTIONS OF 2,3,4,6-TETRA-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE

PROCEDURES FOR CONDUCTING THE REACTIONS

The procedures used to conduct the reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide were essentially the same as those described previously for reactions of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide which were analyzed by polarimetry and GLC. The glassware was dried in the same manner and the solutions were prepared in a dry atmosphere.

Mercuric cyanide was dissolved in the nitromethane (35 ml) by refluxing. Subsequent to distilling off of the nitromethane, cyclohexanol was weighed into the cool 50-ml volumetric flask. Benzene (35 ml) was transferred into a second 50-ml volumetric flask. Subsequent to distilling off 10 ml of the benzene, 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide was weighed into the flask containing the benzene.

The two volumetric flasks were allowed to thermally equilibrate at the desired reaction temperature in a bath for 30 minutes. A connecting tube was placed between the flasks and the contents of the two flasks were mixed together. A sampling chamber (29) was attached to the flask containing the reaction solution and the flask was returned to the water bath. Time zero for the reaction was taken to be the point at which the mixing of the nitromethane and benzene solutions began.

POLARIMETRIC ANALYSIS

The procedure for analyzing the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reactions by polarimetry was the same as that described previously for reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide. The polarimetric data obtained for these reactions are given in Appendix IV.

CARBOHYDRATE ANALYSIS

Product Identification

The reactant and carbohydrate products of the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reactions were identified and measured quantitatively by GLC. Prior to the GLC analysis, the reaction samples were subjected to a series of chemical reactions in which the unreacted glucosyl bromide was converted to phenyl 2,3,4,6-tetra-O-methyl-1-thio-β-D-glucopyranoside and

hydroxyl groups were subsequently propionylated. (The procedure is given under Quantitative Measurement Procedure.)

Chromatogram E (Fig. 19) illustrates a GLC analysis (Conditions C) of a synthetic mixture of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide and its expected reaction products subjected to the procedure. The identities of the peaks are as follows:

(1) n-butyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside (internal standard),

(2) 2,3,4,6-tetra-O-methyl-D-glucopyranose (as the 1-O-propionyl derivative, this compound would result from hydrolysis of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide),

(3) cyclohexyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside,

(4) cyclohexyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside, and

(5) phenyl 2,3,4,6-tetra-O-methyl-1-thio-β-D-glucopyranoside.

Chromatograms F and G (Fig. 20) are reproductions of chromatograms obtained from analysis of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reactions. Chromatogram F illustrates analysis of a reaction in which the glucosyl bromide has completely reacted. Chromatogram G illustrates analysis of the ratio of anomeric glucosides in a partially completed reaction. (See Appendix IX for procedure.)

Quantitative Measurement Procedure

Aliquots (5 ml) taken during the reaction for determining the ratio of anomeric glucosides as a function of time were pipeted into a solution (0.66 ml) of methanolic sodium methoxide (0.5M)-thiophenol (10/1, v/v). Aliquots (5 ml) of the reactions taken after the glucosyl bromide had completely

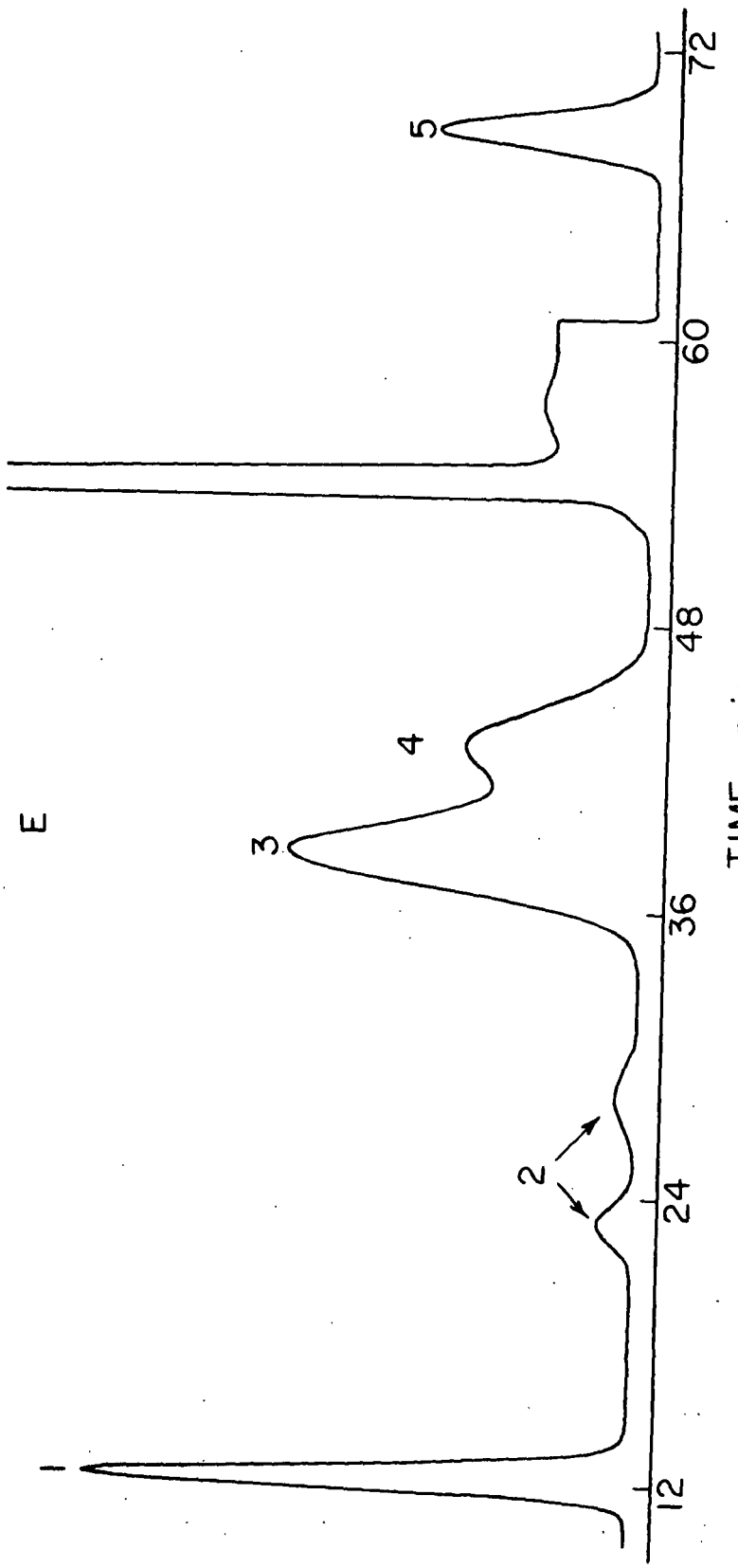


Figure 19. Sample Chromatogram of a Synthetic Mixture of Carbohydrates in the 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl Bromide Reaction; GLC Conditions C

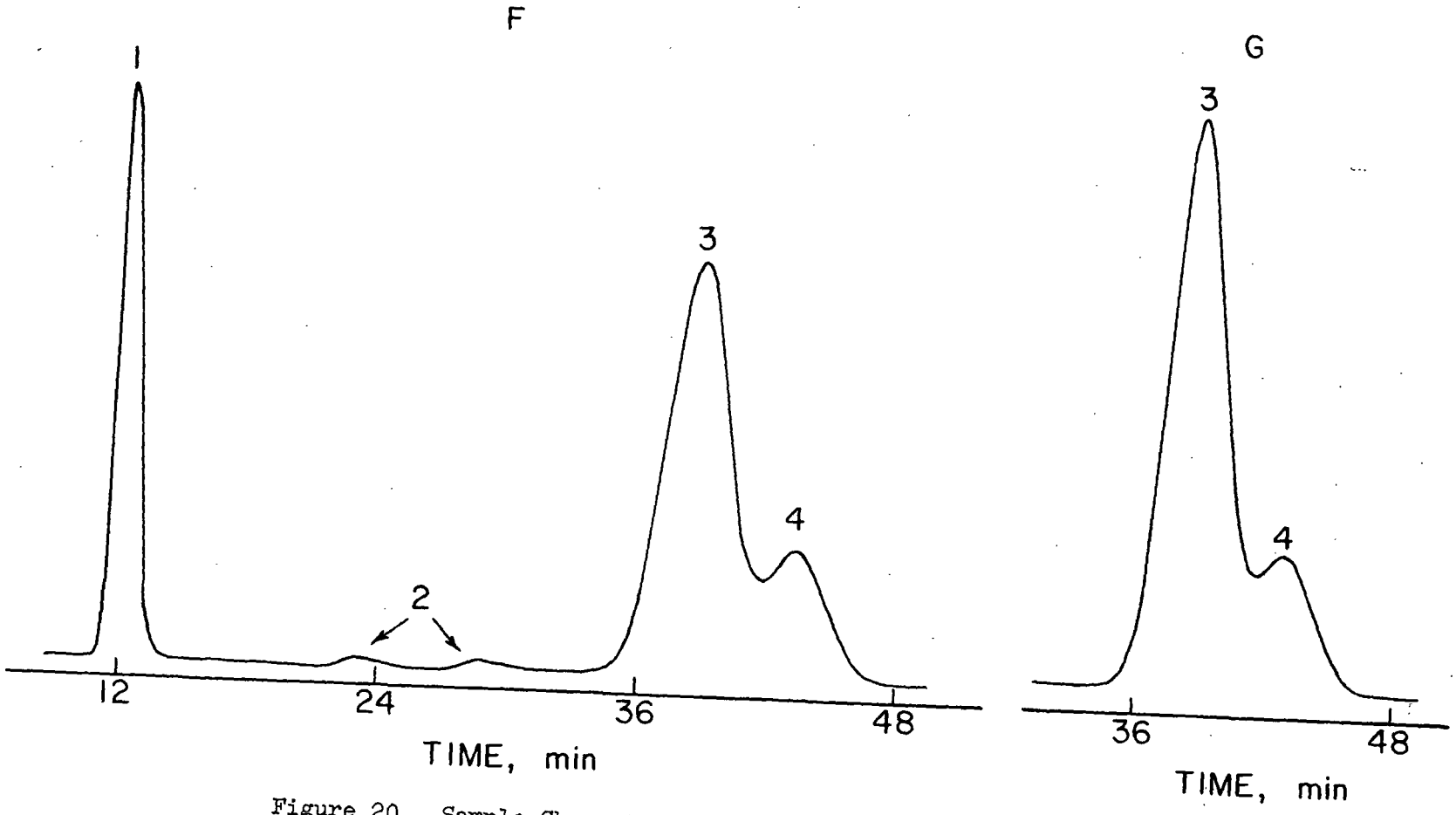


Figure 20. Sample Chromatograms of Carbohydrates in the Reaction of 2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl Bromide; F, Completed Reaction; G, Partially Completed Reaction; GLC Conditions C

reacted were transferred to a 10-ml Erlenmeyer flask. The samples were sealed against moisture and placed in the refrigerator.

The desired amount of a standard solution (0.054M) of internal standard, n-butyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside, was added to the samples which were then concentrated *in vacuo* to an oil. The oil was propionylated with propionic anhydride-pyridine (*ca.* 2.0 ml; 1/2, v/v) as described previously[1], dissolved in chloroform (*ca.* 0.5 ml) and analyzed by GLC (Conditions C). The required GLC response factors and a description for their use in calculating the mole fraction of products in the reaction samples are given in Appendix IX.

[1]See Procedure A under Quantitative Measurement Procedures for the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide.

NOMENCLATURE

α-Cyc 2-OAc	Cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranoside
β-Cyc 2-OAc	Cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside
α-Cyc 2-OH	Cyclohexyl 3,4,6-tri-O-methyl-α-D-glucopyranoside
β-Cyc 2-OH	Cyclohexyl 3,4,6-tri-O-methyl-β-D-glucopyranoside
α-Cyc T_4MG	Cyclohexyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside
β-Cyc T_4MG	Cyclohexyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside
GLC	Gas-liquid chromatography
Hydrolysis product[1]	1-O- and 2-O-Acetyl-3,4,6-tri-O-methyl-D-glucopyranose
NMR	Nuclear magnetic resonance spectroscopy
OE	1,2-O-(1-Cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose
Phenyl 1-S-2-OAc	Phenyl 2-O-acetyl-3,4,6-tri-O-methyl-1-thio-β-D-glucopyranoside
Phenyl 1-S T_4MG	Phenyl 2,3,4,6-tetra-O-methyl-1-thio-β-D-glucopyranoside
1-O-Propionyl T_4MG	2,3,4,6-Tetra-O-methyl-1-O-propionyl-D-glucopyranose
Reducing sugar[2]	2,3,4,6-Tetra-O-methyl-D-glucopyranose
TLC	Thin-layer chromatography
TMG	3,4,6-Tri-O-methyl-D-glucopyranose

[1]As used in describing the reaction products of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide reaction.

[2]As used in describing the reaction products of the 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide reaction.

ACKNOWLEDGMENTS

The author acknowledges the gifts and continual guidance of God.

For her help in the preparation of this manuscript, and for her encouragement, prayers, and sacrifices, the author wishes to thank his wife, Rita.

The author gratefully acknowledges the assistance of his thesis advisory committee: Drs. L. R. Schroeder (Chairman), D. C. Johnson, and R. D. McKelvey. In particular, the author is grateful to Dr. L. R. Schroeder for his encouragement, constructive criticisms, and helpful discussions. The author also wishes to thank the many other faculty members, staff personnel, and fellow students who provided valuable assistance during the course of this work.

The author recognizes and acknowledges the support of the Institute's member companies which supported this work through their contributions to The Institute of Paper Chemistry.

LITERATURE CITED

1. Schroeder, L. R. The alcoholysis of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide. Doctoral Dissertation. Appleton, WI, The Institute of Paper Chemistry, 1965. 159 p.

2. Overend, W. G. Glycosides. In The carbohydrates: chemistry and biochemistry. 2nd ed. Vol. 1A. p. 279. New York, Academic Press, Inc., 1972.

3. Rudie, G. F. Koenigs-Knorr synthesis of β-1,4-linked disaccharides. Doctoral Dissertation. Appleton, WI, The Institute of Paper Chemistry, 1973. 113 p.

4. Evans, W. L., Reynolds, D. D., and Talley, E. A., Adv. Carbohyd. Chem., 6:41(1951).

5. Haynes, L. J., and Newth, F. H., Adv. Carbohyd. Chem., 10:207(1955).

6. Capon, B., Chem. Rev., 69:407(1969).

7. Helferich, B., and Wedemeyer, K. F., Ann., 563:139(1949).

8. Bernstein, S., and Conrow, R. B., J. Org. Chem., 36:863(1971).

9. Reynolds, D. D., and Evans, W. L., J. Am. Chem. Soc., 60:2559(1938).

10. Schroeder, L. R., and Green, J. W., J. Chem. Soc. (C) 1966:530.

11. Koenigs, W., and Knorr, E., Ber. 34:957(1901).

12. Talley, E. A., Methods Carbohyd. Chem., 2:337(1963).

13. Hough, L., and Richardson, A. C. The monosaccharides: pentoses, hexoses, heptoses and higher sugars. In Rodd's Chemistry of carbon compounds. 2nd ed. Vol. 1F. p. 327. Amsterdam, Elsevier Publishing Co., 1967.

14. Rhind-Tutt, A. J., and Vernon, C. A., J. Chem. Soc., 1960:4637.

15. Flowers, H. M., Carbohyd. Res., 18:211(1971).

16. Ishikawa, T., and Fletcher, H. G., Jr., J. Org. Chem., 34:563(1969).

17. Wallace, J. E. Unpublished work, The Institute of Paper Chemistry, 1973.

18. Frush, H. L., and Isbell, H. S., J. Res. Natl. Bur. Std., 27:413(1941).

19. Frush, H. L., and Isbell, H. S., J. Res. Natl. Bur. Std., 35:111(1945).

20. Frush, H. L., and Isbell, H. S., J. Res. Natl. Bur. Std., 43:161(1949).

21. Newth, F. H., and Phillips, G. O., J. Chem. Soc., 1953:2896.

22. Newth, F. H., and Phillips, G. O., J. Chem. Soc., 1953:2900.

23. Newth, F. H., and Phillips, G. O., J. Chem. Soc., 1953:2904.

24. Mattok, G. L., and Phillips, G. O., J. Chem. Soc., 1956:1836.

25. Mattok, G. L., and Phillips, G. O., J. Chem. Soc., 1958:130.

26. Capon, B., Collins, P. M., Levy, A. A., and Overend, W. G., J. Chem. Soc., 1964:3242.

27. Chapman, N. B., and Laird, W. E., Chem. and Ind., 1954:20.

28. Wolfrom, M. L., and Thompson, A. Glycosides, simple acetals, and thioacetals. In The carbohydrates: chemistry, biochemistry, and physiology. p. 188. New York, Academic Press, Inc., 1957.

29. Hultman, D. P. Ethanolyses of 3,4,6-tri-O-methyl-1,2-O-(alkyl ortho-acetyl)-α-D-glucopyranoses. Doctoral Dissertation. Appleton, WI, The Institute of Paper Chemistry, 1970. 171 p.

30. Counts, K. M. Alcoholyses of 2,3,4-tri-O-acetyl-α-D-xylopyranosyl bromide and 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide. Doctoral Dissertation. Appleton, WI, The Institute of Paper Chemistry, 1974. 131 p.

31. Schroeder, L. R., Green, J. W., and Johnson, D. C., J. Chem. Soc. (B), 1966:447.

32. Bethell, D., and Gold, V. Carbonium ion: an introduction. New York, Academic Press, 1967. 387 p.

33. Szwarc, M. Concept of ion pairs. In Ions and ion pairs in organic reactions. Vol. 1. p. 1. New York, John Wiley and Sons, Inc., 1972.

34. Kochetkov, N. K., Khorlin, A. J., and Bochkov, A. F., Tetrahedron, 23:693(1967).

35. Dykes, C. A. Acid-catalyzed reactions of 1,2-O-(1-exo-ethoxyethylidene)-3,4,6-tri-O-methyl-α-D-mannopyranose with ethanol. Doctoral Dissertation. Appleton, WI, The Institute of Paper Chemistry, 1975. 140 p.

36. Kosower, E. M. An introduction to physical organic chemistry. p. 49. New York, John Wiley and Sons, Inc., 1968.

37. Evans, D., and Reynolds, W., J. Am. Chem. Soc., 58:797, 1661(1936).

38. Lund, H., and Bjerrum, J., Ber., 64:210(1931).

39. Wolfrom, M. L., and Thompson, A., Methods Carbohyd. Chem., 2:211(1963).

40. Hultman, D. P., Schroeder, L. R., and Haigh, F. C., J. Chem. Soc., Perkin II, 1972:1525.

41. West, E. S., and Holden, R. F., Organic Synthesis, 20:97(1940).

42. Schroeder, L. R., Hultman, D. P., and Johnson, D. C., J. Chem. Soc., Perkin II, 1972:1068.

43. Sundberg, R. L., McCloskey, C. M., Rees, D. E., and Coleman, G. H., J. Am. Chem. Soc., 67:1080(1945).

44. Schroeder, L. R., Unpublished work, The Institute of Paper Chemistry.

45. Seib, P. A., Carbohyd. Res., 8:101(1968).

46. Rowell, R. M., Carbohyd. Res., 23:417(1972).

47. Zgol, R. Acid-catalyzed methanolyses of 1,2-O-alkylidene- and -arylidene-3,4,6-tri-O-methyl-α-D-glucopyranoses. Doctoral Dissertation. Appleton, WI, The Institute of Paper Chemistry, 1974. 197 p.

48. Glasstone, S., Laidler, K. J., and Eyring, H. The theory of rate processes. New York, McGraw-Hill Book Company, Inc., 1941. 611 p.

APPENDIX I

PRODUCT ANALYSES FOR REACTIONS OF 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE

The initial product distributions of the reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide in which various reaction temperatures, cyclohexanol concentrations, mercuric cyanide concentrations, and glucosyl bromide concentrations were employed are given in Table XX.

The final product analyses of the reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide which were conducted in the kinetic study are given in Table XXI. The reaction samples, from which these product analyses were determined, were obtained after a minimum of 10 hours reaction time.

TABLE XX

DATA FOR DETERMINING THE INITIAL PRODUCT DISTRIBUTIONS FOR THE REACTIONS OF 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE WITH CYCLOHEXANOL IN THE PRESENCE OF MERCURIC CYANIDE EMPLOYING VARIOUS CONCENTRATIONS OF REACTANTS

Temp., °C	Glucosyl Bromide (10^3M)	Cyclohexanol (10^2M)	$Hg(CN)_2$ (10^3M)	Time, min	Reaction, %[a]	Mole Fraction[b] α-Cyc 2-OAc	Mole Fraction[b] β-Cyc 2-OAc	Mole Fraction[b] OE
10	5.451	9.962	6.161	15	6	0.07	0.60	0.33
				30	14	0.08	0.56	0.36
				51	26	0.06	0.56	0.38
10	2.872	9.368	6.107	15	2	0.05	0.54	0.42
				30	5	0.06	0.49	0.45
				45	9	0.06	0.53	0.42
10	2.248	4.695	5.979	19	3	0.10	0.47	0.43
				41	8	0.13	0.44	0.44
				60	13	0.10	0.45	0.46
10	5.506	17.978	6.000	15	5	0.04	0.82	0.14
				26	11	0.04	0.81	0.15
				35	20	0.04	0.84	0.12
10	5.825	9.094	3.000	30	2	0.08	0.56	0.34
				45	4	0.06	0.61	0.36
10	6.076	9.100	12.092	16	6	0.06	0.58	0.37
				25	10	0.05	0.62	0.34
				35	15	0.06	0.64	0.30
25	4.921	6.660	4.433	15	7	0.08	0.52	0.40
				25	14	0.08	0.54	0.39
				35	25	0.08	0.58	0.34
20	5.494	8.851	5.915	15	6	0.06	0.56	0.38
				25	13	0.07	0.57	0.37
				35	22	0.05	0.57	0.39
15	4.378	6.644	4.472	15	2	0.07	0.58	0.35
				30	5	0.07	0.57	0.36
				45	9	0.07	0.58	0.35

[a] Calculated from the polarimetric data (Appendix II) and Equation (6).

[b] Glucose product mole fraction which has appeared at time t. See Nomenclature for compound names.

TABLE XXI

FINAL PRODUCT ANALYSES FOR REACTIONS OF 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE CONDUCTED IN THE KINETIC STUDY[a]

Reaction Number[b]	Glucosyl Bromide (10^3M)	Cyclohexanol (10^2M)	$Hg(CN)_2$ (10^3M)	Temp., °C	Products[c]					Total Measured
					Hydrolysis Product	α-Cyc 2-OAc	β-Cyc 2-OAc	α-Cyc 2-OH	β-Cyc 2-OH	
1	6.802	8.944	5.986	10.0	0.15	0.05	0.80	0.01	0.01	1.02
2	3.142	10.029	5.998	10.1	0.13	0.04	0.83	0.01	0.01	1.02
3	6.063	4.883	6.185	10.0	0.17	0.06	0.79	Trace	Trace	1.02
4	5.786	13.474	6.100	10.0	0.15	0.04	0.78	0.02	0.02	1.01
5	6.320	18.253	5.839	10.0	0.12	0.04	0.82	0.01	0.02	1.01
6	6.158	9.465	2.981	10.1	0.14	0.02	0.83	Trace	Trace	0.99
7	5.852	8.990	12.083	10.1	0.16	0.05	0.79	0.01	0.01	1.02
8	4.405	6.541	4.523	25.0	0.15	0.05	0.82	0.02	0.02	1.06
9	4.328	6.957	4.408	20.0	0.14	0.04	0.80	Trace	Trace	0.98
10	5.542	8.967	5.981	20.0	0.14	0.05	0.90	Trace	Trace	1.09
11	4.405	6.680	4.420	15.0	0.15	0.04	0.80	0.01	0.01	1.00
12	4.706	6.757	4.513	10.0	0.12	0.03	0.83	Trace	0.01	0.99
13	4.401	6.658	(4.621)[d]	10.0	0.06	0.03	0.86	0.01	0.04	0.99

[a] GLC product analyses of final reaction samples obtained after a minimum of 10 hours reaction time. Analyses of samples containing known concentrations of these compounds indicated that the mole fraction of each glucosidic product could be determined within ±2 mole%.

[b] Reaction numbers correspond to polarimetric data given in Appendix II.

[c] See Nomenclature for compound names.

[d] Mercuric bromide was used in place of mercuric cyanide.

APPENDIX II

POLARIMETRIC DATA FOR THE 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE REACTIONS

This appendix contains the polarimetric data for reactions of 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide. The data were used in conjunction with Equation (6) to calculate the initial rates of the reactions. The computed value of the initial rate is given for each reaction. Optical rotations were measured on a Perkin Elmer 141 MC polarimeter using a mercury lamp at 546.1 nm.

TABLE XXII

REACTION NO. 1: GLUCOSYL BROMIDE, 6.802×10^{-3}M; CYCLOHEXANOL, 8.944×10^{-2}M; MERCURIC CYANIDE, 5.986×10^{-3}M; TEMP, 10.0°C; $(dH/dt)_{t=0}$, 1.544×10^{-7}MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.665	6.75	0.660	13.00	0.653	29.00	0.631
1.25	0.665	7.00	0.660	13.50	0.652	30.00	0.630
1.50	0.665	7.25	0.660	14.00	0.652	32.00	0.628
1.75	0.664	7.50	0.659	14.50	0.651	34.00	0.625
2.00	0.664	7.75	0.659	15.00	0.651	36.00	0.621
2.25	0.664	8.00	0.659	15.50	0.650	38.00	0.618
2.50	0.664	8.25	0.659	16.00	0.650	40.00	0.614
2.75	0.664	8.50	0.659	16.50	0.649	42.00	0.610
3.00	0.663	8.75	0.658	17.00	0.648	44.00	0.605
3.25	0.663	9.00	0.658	17.50	0.648	46.00	0.601
3.50	0.663	9.25	0.658	18.00	0.647	50.00	0.592
3.75	0.663	9.50	0.657	18.50	0.647	55.00	0.578
4.00	0.662	9.75	0.657	19.00	0.646	60.00	0.562
4.25	0.662	10.00	0.657	19.50	0.645	70.00	0.520
4.50	0.662	10.25	0.656	20.00	0.644	80.00	0.461
4.75	0.661	10.50	0.656	21.00	0.643	90.00	0.377
5.00	0.662	10.75	0.656	22.00	0.641	100.00	0.272
5.25	0.661	11.00	0.655	23.00	0.640	110.00	0.618
5.50	0.661	11.25	0.655	24.00	0.639	120.00	0.091
5.75	0.661	11.50	0.655	25.00	0.638	140.00	0.022
6.00	0.661	11.75	0.655	26.00	0.636	152.00	0.009
6.25	0.661	12.00	0.654	27.00	0.634	α_∞	-0.006
6.50	0.660	12.50	0.654	28.00	0.633		

TABLE XXIII

REACTION NO. 2: GLUCOSYL BROMIDE, 3.142×10^{-3}M; CYCLOHEXANOL, 10.029×10^{-2}M; MERCURIC CYANIDE, 5.998×10^{-3}M; TEMP, 10.1°C; $(dH/dt)_{t=0}$, 7.502×10^{-7}MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.316	7.25	0.313	14.00	0.309	36.00	0.297
1.25	0.316	7.50	0.313	14.50	0.309	38.00	0.296
1.50	0.316	7.75	0.313	15.00	0.309	40.00	0.294
1.75	0.316	8.00	0.313	15.50	0.308	42.00	0.293
2.00	0.316	8.25	0.313	16.00	0.308	44.00	0.291
2.25	0.315	8.50	0.313	16.50	0.307	46.00	0.290
2.50	0.315	8.75	0.312	17.00	0.307	50.00	0.287
2.75	0.315	9.00	0.313	17.50	0.307	55.00	0.284
3.00	0.315	9.25	0.312	18.00	0.307	60.00	0.280
3.25	0.315	9.50	0.312	18.50	0.306	70.00	0.272
3.50	0.315	9.75	0.312	19.00	0.306	80.00	0.260
3.75	0.315	10.00	0.312	19.50	0.306	90.00	0.250
4.00	0.315	10.25	0.312	20.00	0.306	100.00	0.240
4.25	0.315	10.50	0.312	21.00	0.305	110.00	0.226
4.50	0.314	10.75	0.312	22.00	0.304	120.00	0.212
4.75	0.314	11.00	0.312	23.00	0.304	130.00	0.182
5.00	0.314	11.25	0.311	24.00	0.304	140.00	0.165
5.25	0.314	11.50	0.311	25.00	0.303	150.00	0.147
5.50	0.314	11.75	0.311	26.00	0.303	170.00	0.109
5.75	0.314	12.00	0.311	27.00	0.302	190.00	0.078
6.00	0.314	12.25	0.311	28.00	0.302	210.00	0.053
6.25	0.313	12.50	0.310	29.00	0.301	220.00	0.045
6.50	0.314	12.75	0.310	30.00	0.301	α_∞	-0.003
6.75	0.314	13.00	0.310	32.00	0.299		
7.00	0.313	13.50	0.310	34.00	0.298		

TABLE XXIV

REACTION NO. 3: GLUCOSYL BROMIDE, 5.803×10^{-3}M; CYCLOHEXANOL, 4.938×10^{-2}M; MERCURIC CYANIDE, 6.038×10^{-3}M; TEMP, 10.0°C; $(dH/dt)_{t=0}$, 1.424×10^{-7}MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.589	7.25	0.584	13.50	0.579	32.00	0.560
1.25	0.588	7.50	0.583	13.75	0.578	34.00	0.557
1.50	0.588	7.75	0.583	14.00	0.578	36.00	0.557
1.75	0.587	8.00	0.583	14.25	0.578	38.00	0.554
2.00	0.588	8.25	0.583	14.50	0.578	40.00	0.552
2.25	0.588	8.50	0.583	14.75	0.577	42.00	0.550
2.50	0.587	8.75	0.582	15.00	0.577	44.00	0.548
2.75	0.587	9.00	0.582	15.50	0.577	46.00	0.546
3.00	0.587	9.25	0.582	16.00	0.576	50.00	0.543
3.25	0.587	9.50	0.582	16.50	0.576	55.00	0.537
3.50	0.587	9.75	0.582	17.00	0.575	60.00	0.532
3.75	0.586	10.00	0.582	17.50	0.575	65.00	0.526
4.00	0.586	10.25	0.581	18.00	0.575	70.00	0.521
4.25	0.586	10.50	0.581	18.50	0.574	75.00	0.513
4.50	0.586	10.75	0.581	19.00	0.574	80.00	0.503
4.75	0.586	11.00	0.581	19.50	0.573	90.00	0.479
5.00	0.585	11.25	0.581	20.00	0.573	100.00	0.447
5.25	0.585	11.50	0.580	21.00	0.572	110.00	0.410
5.50	0.585	11.75	0.580	22.00	0.571	120.00	0.365
5.75	0.585	12.00	0.580	23.00	0.571	130.00	0.309
6.00	0.585	12.25	0.580	24.00	0.569	150.00	0.189
6.25	0.585	12.50	0.579	25.00	0.568	170.00	0.092
6.50	0.584	12.75	0.579	26.00	0.567	190.00	0.044
6.75	0.584	13.00	0.579	28.00	0.564	220.00	0.017
7.00	0.584	13.25	0.579	30.00	0.562	α_∞	-0.002

TABLE XXV

REACTION NO. 4: GLUCOSYL BROMIDE, 5.786×10^{-3}M; CYCLOHEXANOL, 13.474×10^{-2}M; MERCURIC CYANIDE, 6.100×10^{-3}M; TEMP, 10.0°C; $(dH/dt)_{t=0}$, 1.463×10^{-7}MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.554	6.50	0.549	11.50	0.544	26.00	0.525
1.25	0.553	6.75	0.549	11.75	0.544	28.00	0.532
1.50	0.553	7.00	0.549	12.00	0.543	30.00	0.520
1.75	0.553	7.25	0.548	12.50	0.543	32.00	0.517
2.00	0.553	7.50	0.548	13.00	0.542	34.00	0.514
2.25	0.553	7.75	0.548	13.50	0.542	36.00	0.511
2.50	0.552	8.00	0.548	14.00	0.541	38.00	0.508
3.00	0.552	8.25	0.548	14.50	0.540	40.00	0.504
3.25	0.552	8.50	0.547	15.00	0.540	42.00	0.500
3.50	0.552	8.75	0.547	15.50	0.539	44.00	0.497
3.75	0.551	9.00	0.547	16.00	0.539	46.00	0.492
4.00	0.551	9.25	0.547	16.50	0.538	50.00	0.478
4.25	0.551	9.50	0.546	17.00	0.537	55.00	0.470
4.50	0.551	9.75	0.546	17.50	0.536	60.00	0.455
4.75	0.551	10.00	0.546	18.00	0.536	70.00	0.418
5.00	0.550	10.25	0.545	18.50	0.535	80.00	0.363
5.25	0.550	10.50	0.545	19.00	0.534	90.00	0.291
5.50	0.550	10.75	0.545	20.00	0.533	110.00	0.127
5.75	0.550	11.00	0.545	22.00	0.531	120.00	0.051
6.00	0.549	11.25	0.544	24.00	0.528	150.00	0.012
6.25	0.549					α_∞	-0.005

TABLE XXVI

REACTION NO. 5: GLUCOSYL BROMIDE, 6.320×10^{-3}M; CYCLOHEXANOL, 18.253×10^{-2}M; MERCURIC CYANIDE, 5.839×10^{-3}M; TEMP 10.0°C; $(dH/dt)_{t=0}$, 1.480×10^{-7} MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.636	6.00	0.630	11.00	0.623	24.00	0.601
1.25	0.636	6.25	0.629	11.25	0.623	26.00	0.596
1.50	0.636	6.50	0.629	11.50	0.622	28.00	0.592
1.75	0.636	6.75	0.629	11.75	0.622	30.00	0.587
2.00	0.635	7.00	0.629	12.00	0.621	32.00	0.582
2.25	0.635	7.25	0.628	12.50	0.621	34.00	0.576
2.50	0.635	7.50	0.628	13.00	0.620	36.00	0.670
2.75	0.635	7.75	0.628	13.50	0.619	38.00	0.562
3.00	0.634	8.00	0.627	14.00	0.618	40.00	0.555
3.25	0.634	8.25	0.627	14.50	0.618	45.00	0.533
3.50	0.634	8.50	0.626	15.00	0.617	50.00	0.505
3.75	0.633	8.75	0.626	15.50	0.616	56.00	0.460
4.00	0.633	9.00	0.626	16.00	0.616	60.00	0.420
4.25	0.633	9.25	0.625	17.00	0.614	66.00	0.345
4.50	0.632	9.50	0.625	18.00	0.612	70.00	0.284
4.75	0.632	9.75	0.625	19.00	0.610	75.00	0.208
5.00	0.632	10.00	0.624	20.00	0.608	80.00	0.133
5.25	0.631	10.25	0.624	21.00	0.606	90.00	0.043
5.50	0.631	10.50	0.624	22.00	0.605	110.00	-0.005
5.75	0.630	10.75	0.623	23.00	0.602	α_∞	-0.010

TABLE XXVII

REACTION NO. 6: GLUCOSYL BROMIDE, 6.158×10^{-3}M; CYCLOHEXANOL, 9.465×10^{-2}M; MERCURIC CYANIDE, 2.981×10^{-3}M; TEMP, 10.1°C; $(dH/dt)_{t=0}$, 7.815×10^{-8} MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.603	7.50	0.600	13.75	0.597	30.00	0.590
1.25	0.602	7.75	0.600	14.00	0.597	32.00	0.589
1.50	0.602	8.00	0.600	14.25	0.597	34.00	0.588
1.75	0.602	8.25	0.599	14.50	0.596	36.00	0.587
2.00	0.602	8.50	0.599	14.75	0.597	38.00	0.586
2.25	0.602	8.75	0.599	15.00	0.596	40.00	0.585
2.50	0.602	9.00	0.599	15.50	0.596	42.00	0.583
2.75	0.602	9.25	0.599	16.00	0.596	44.00	0.582
3.00	0.602	9.50	0.599	16.50	0.596	46.00	0.581
3.25	0.602	9.75	0.599	17.00	0.596	50.00	0.577
3.50	0.601	10.00	0.598	17.50	0.596	55.00	0.573
3.75	0.601	10.25	0.598	18.00	0.596	60.00	0.569
4.00	0.601	10.50	0.598	18.50	0.595	70.00	0.557
4.25	0.601	10.75	0.598	19.00	0.595	80.00	0.540
4.50	0.601	11.00	0.598	19.50	0.595	90.00	0.509
4.75	0.601	11.25	0.598	20.00	0.595	100.00	0.476
5.00	0.601	11.50	0.598	21.00	0.594	110.00	0.400
5.25	0.601	11.75	0.598	22.00	0.594	120.00	0.307
5.50	0.601	12.00	0.598	23.00	0.594	130.00	0.182
5.75	0.601	12.25	0.598	24.00	0.593	140.00	0.081
6.00	0.600	12.50	0.597	25.00	0.592	150.00	0.031
6.25	0.600	12.75	0.597	26.00	0.592	170.00	0.005
6.50	0.600	13.00	0.597	27.00	0.592	α_∞	-0.005
6.75	0.600	13.25	0.597	28.00	0.591		
7.00	0.600	13.50	0.597	29.00	0.591		
7.25	0.600						

TABLE XXVIII

REACTION NO. 7: GLUCOSYL BROMIDE, 5.852×10^{-3}M; CYCLOHEXANOL, 8.990×10^{-2}M; MERCURIC CYANIDE, 12.083×10^{-3}M; TEMP, 10.1°C; $(dH/dt)_{t=0}$, 3.163×10^{-7} MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.584	6.25	0.575	13.00	0.559	34.00	0.504
1.25	0.584	6.50	0.574	13.50	0.558	36.00	0.498
1.50	0.583	6.75	0.574	14.00	0.557	38.00	0.490
1.75	0.583	7.00	0.573	14.50	0.556	40.00	0.484
2.00	0.583	7.25	0.572	15.00	0.553	42.00	0.478
2.25	0.582	7.50	0.571	16.00	0.550	44.00	0.472
2.50	0.582	7.75	0.571	17.00	0.548	46.00	0.468
2.75	0.581	8.00	0.570	18.00	0.546	50.50	0.454
3.00	0.581	8.25	0.570	19.00	0.544	55.00	0.434
3.25	0.580	8.50	0.569	20.00	0.542	60.50	0.409
3.50	0.580	8.75	0.569	21.00	0.540	73.00	0.340
3.75	0.579	9.00	0.568	22.00	0.537	83.00	0.278
4.00	0.579	9.25	0.568	23.00	0.534	93.00	0.209
4.25	0.578	9.50	0.567	24.00	0.532	103.00	0.145
4.50	0.578	9.75	0.566	25.00	0.530	113.00	0.100
4.75	0.578	10.00	0.566	26.00	0.528	128.00	0.056
5.00	0.577	10.50	0.565	27.00	0.524	148.00	0.032
5.25	0.577	11.00	0.563	28.00	0.522	168.00	0.018
5.50	0.576	11.50	0.562	29.00	0.520	α_∞	-0.006
5.75	0.576	12.00	0.561	30.00	0.516		
6.00	0.575	12.50	0.560	32.00	0.511		

TABLE XXIX

REACTION NO. 8: GLUCOSYL BROMIDE, 4.405×10^{-3}, CYCLOHEXANOL, 6.541×10^{-2}M; MERCURIC CYANIDE, 4.523×10^{-3}M; TEMP, 25.0°C; $(dH/dt)_{t=0}$, 2.803×10^{-7} MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.452	6.50	0.444	12.50	0.431	27.00	0.390
1.25	0.452	6.75	0.443	13.00	0.431	28.00	0.386
1.50	0.452	7.00	0.443	13.50	0.430	29.00	0.381
1.75	0.451	7.25	0.442	14.00	0.429	30.00	0.377
2.00	0.451	7.50	0.442	14.50	0.428	32.00	0.368
2.25	0.450	7.75	0.442	15.00	0.427	34.00	0.356
2.50	0.450	8.00	0.441	15.50	0.425	36.00	0.344
2.75	0.450	8.25	0.441	16.00	0.424	38.00	0.330
3.00	0.449	8.50	0.440	16.50	0.422	40.00	0.314
3.25	0.449	8.75	0.440	17.00	0.421	42.00	0.297
3.50	0.449	9.00	0.439	17.50	0.420	44.00	0.278
3.75	0.448	9.25	0.439	18.00	0.419	46.00	0.259
4.00	0.448	9.75	0.438	18.50	0.418	50.00	0.214
4.25	0.447	10.00	0.438	19.00	0.416	55.00	0.155
4.50	0.447	10.25	0.437	19.50	0.415	60.00	0.107
4.75	0.446	10.50	0.436	20.00	0.414	70.00	0.047
5.00	0.446	10.75	0.436	21.00	0.411	80.00	0.025
5.25	0.446	11.00	0.435	22.00	0.407	90.00	0.016
5.50	0.445	11.25	0.435	23.00	0.404	100.00	0.008
5.75	0.445	11.50	0.435	24.00	0.400	α_∞	-0.005
6.00	0.444	11.75	0.434	25.00	0.397		
6.25	0.444	12.00	0.433	26.00	0.394		

TABLE XXX

REACTION NO. 9: GLUCOSYL BROMIDE, 4.328×10^{-3}M; CYCLOHEXANOL, 6.957×10^{-2}M; MERCURIC CYANIDE, 4.408×10^{-3}M; TEMP, 20.0°C; $(dH/dt)_{t=0}$, 1.655×10^{-7} MOLExLIT^{-1}SEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.421	6.50	0.416	12.00	0.410	26.00	0.392
1.25	0.421	6.75	0.415	12,50	0.409	27.00	0.391
1.50	0.420	7.00	0.415	13.00	0.408	28.00	0.389
1.75	0.420	7.25	0.415	13.50	0.408	29.00	0.388
2.00	0.420	7.50	0.415	14.00	0.407	30.00	0.387
2.25	0.419	7.75	0.414	14.50	0.407	32.00	0.383
2.50	0.419	8.00	0.414	15.00	0.406	34.00	0.380
2.75	0.419	8.25	0.414	15.50	0.406	36.00	0.376
3.00	0.419	8.50	0.414	16.00	0.405	38.00	0.372
3.25	0.419	8.75	0.413	16.50	0.405	40.00	0.367
3.50	0.418	9.00	0.413	17.00	0.404	42.00	0.363
3.75	0.418	9.25	0.413	17.50	0.404	44.00	0.358
4.00	0.418	9.50	0.412	18.00	0.403	46.00	0.353
4.25	0.418	9.75	0.412	18.50	0.402	50.00	0.342
4.50	0.417	10.00	0.412	19.00	0.401	55.00	0.325
4.75	0.417	10.25	0.412	19.50	0.401	60.00	0.306
5.00	0.417	10.50	0.411	20.00	0.400	70.00	0.255
5.25	0.417	10.75	0.411	21.00	0.399	80.00	0.189
5.50	0.417	11.00	0.411	22.00	0.398	90.00	0.120
5.75	0.416	11.25	0.411	23.00	0.397	105.00	0.051
6.00	0.416	11.50	0.410	24.00	0.395	120.00	0.023
6.25	0.416	11.75	0.410	25.00	0.393	α_∞	-0.003

TABLE XXXI

REACTION NO. 10: GLUCOSYL BROMIDE, 5.542×10^{-3}M; CYCLOHEXANOL, 8.967×10^{-2}M; MERCURIC CYANIDE, 5.981×10^{-3}M; TEMP, 20.0°C; $(dH/dt)_{t=0}$, 2.982×10^{-7} MOLExLIT^{-1}SEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.571	6.00	0.562	12.00	0.547	29.00	0.488
1.25	0.571	6.25	0.562	12.50	0.546	30.00	0.482
1.50	0.570	6.50	0.561	13.00	0.544	32.00	0.470
1.75	0.570	6.75	0.560	13.50	0.543	34.00	0.458
2.00	0.569	7.00	0.560	14.00	0.542	36.00	0.445
2.25	0.569	7.25	0.559	14.50	0.541	38.00	0.429
2.50	0.569	7.50	0.558	15.00	0.539	40.00	0.412
2.75	0.568	7.75	0.558	16.00	0.536	42.00	0.392
3.00	0.568	8.00	0.557	17.00	0.533	44.00	0.370
3.25	0.568	8.25	0.557	18.00	0.531	46.00	0.346
3.50	0.567	8.50	0.557	19.00	0.527	50.00	0.295
3.75	0.567	8.75	0.556	20.00	0.522	55.00	0.223
4.00	0.566	9.00	0.555	21.00	0.519	60.00	0.156
4.25	0.566	9.25	0.554	22.00	0.515	65.00	0.100
4.50	0.565	9.50	0.554	23.00	0.511	70.00	0.062
4.75	0.565	9.75	0.553	24.00	0.508	80.00	0.027
5.00	0.564	10.00	0.552	25.00	0.503	91.00	0.013
5.25	0.564	10.50	0.551	26.00	0.499	103.00	0.007
5.50	0.563	11.00	0.550	27.00	0.495	122.00	0.003
5.75	0.563	11.50	0.549	28.00	0.491	α_∞	-0.002

TABLE XXXII

REACTION NO. 11: GLUCOSY BROMIDE, 4.405×10^{-3}M; CYCLOHEXANOL, 6.680×10^{-2}M; MERCURIC CYANIDE, 4.472×10^{-3}M; TEMP, 15.0°C; $(dH/dt)_{t=0}$, 1.131×10^{-7} MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.449	6.50	0.446	12.00	0.442	32.00	0.426
1.25	0.449	6.75	0.445	12.50	0.442	34.00	0.424
1.50	0.449	7.00	0.445	13.00	0.441	36.00	0.422
1.75	0.449	7.25	0.445	13.50	0.441	38.00	0.420
2.00	0.449	7.50	0.445	14.00	0.441	40.00	0.418
2.25	0.448	7.75	0.445	14.50	0.440	42.00	0.416
2.50	0.448	8.00	0.444	15.00	0.440	44.00	0.414
2.75	0.448	8.25	0.444	16.00	0.439	46.00	0.411
3.00	0.448	8.50	0.444	17.00	0.438	50.00	0.407
3.25	0.448	8.75	0.444	18.00	0.437	55.00	0.400
3.50	0.448	9.00	0.444	19.00	0.437	60.00	0.393
3.75	0.447	9.25	0.444	20.00	0.437	70.00	0.371
4.00	0.447	9.50	0.444	21.00	0.435	80.00	0.345
4.25	0.447	9.75	0.443	22.00	0.434	90.00	0.311
4.50	0.447	10.00	0.443	23.00	0.434	100.00	0.266
4.75	0.447	10.25	0.443	24.00	0.433	115.00	0.183
5.00	0.447	10.50	0.443	25.00	0.432	135.00	0.080
5.25	0.446	10.75	0.443	26.00	0.431	150.00	0.040
5.50	0.446	11.00	0.443	27.00	0.430	175.00	0.021
5.75	0.446	11.25	0.442	28.00	0.430	α_∞	-0.004
6.00	0.446	11.50	0.442	29.00	0.429		
6.25	0.446	11.75	0.442	30.00	0.428		

TABLE XXXIII

REACTION NO. 12: GLUCOSYL BROMIDE, 4.706×10^{-3}M; CYCLOHEXANOL, 6.757×10^{-2}M; MERCURIC CYANIDE, 4.513×10^{-3}M; TEMP, 10.0°C: $(dH/dt)_{t=0}$, 8.618×10^{-8} MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.468	7.25	0.465	13.50	0.462	23.00	0.458
1.25	0.467	7.50	0.465	13.75	0.462	24.00	0.457
1.50	0.468	7.75	0.465	14.00	0.462	26.00	0.456
1.75	0.468	8.00	0.465	14.25	0.462	28.00	0.455
2.00	0.468	8.25	0.465	14.50	0.462	30.00	0.454
2.25	0.467	8.50	0.465	14.75	0.462	32.00	0.452
2.50	0.467	8.75	0.464	15.00	0.462	34.00	0.451
2.75	0.467	9.00	0.464	15.25	0.461	36.00	0.449
3.00	0.467	9.25	0.464	15.50	0.461	38.00	0.448
3.25	0.467	9.50	0.464	15.75	0.461	40.00	0.446
3.50	0.467	9.75	0.464	16.00	0.461	45.00	0.443
3.75	0.467	10.00	0.464	16.25	0.461	50.00	0.440
4.00	0.467	10.25	0.464	16.50	0.461	55.00	0.438
4.25	0.467	10.50	0.464	16.75	0.461	60.00	0.434
4.50	0.466	10.75	0.463	17.00	0.460	70.00	0.427
4.75	0.466	11.00	0.463	17.25	0.460	80.00	0.418
5.00	0.466	11.25	0.463	17.50	0.460	90.00	0.407
5.25	0.466	11.50	0.463	17.75	0.460	100.00	0.394
5.50	0.466	11.75	0.463	18.00	0.460	120.00	0.357
5.75	0.466	12.00	0.463	18.50	0.460	140.00	0.298
6.00	0.466	12.25	0.463	19.00	0.459	160.00	0.217
6.25	0.466	12.50	0.463	19.50	0.459	180.00	0.129
6.50	0.466	12.75	0.463	20.00	0.459	200.00	0.063
6.75	0.465	13.00	0.463	21.00	0.459	220.00	0.029
7.00	0.465	13.25	0.462	22.00	0.458	α_∞	-0.004

TABLE XXXIV

REACTION NO. 13: GLUCOSYL BROMIDE, 4.401×10^{-3}; CYCLOHEXANOL, 6.658×10^{-2}M; MERCURIC BROMIDE, 4.621×10^{-3}M; TEMP, 10.0°C.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.349	3.50	0.224	6.00	0.151	11.00	0.079
1.25	0.334	3.75	0.214	6.25	0.146	12.00	0.071
1.50	0.319	4.00	0.206	6.50	0.141	13.00	0.064
1.75	0.305	4.25	0.199	7.00	0.132	14.00	0.059
2.00	0.292	4.50	0.191	7.50	0.124	16.00	0.049
2.25	0.280	4.75	0.183	8.00	0.117	18.00	0.044
2.50	0.267	5.00	0.176	8.50	0.110	20.00	0.034
2.75	0.255	5.25	0.169	9.00	0.103	α_∞	-0.010
3.00	0.245	5.50	0.163	9.50	0.096		
3.25	0.234	5.75	0.157	10.00	0.090		

APPENDIX III

DERIVATION OF THE EQUATION RELATING THE OPTICAL ROTATION OF THE REACTION MIXTURE TO THE CONCENTRATION OF GLUCOSYL BROMIDE AT TIME t FOR THE 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE REACTION

The first assumption of this derivation is that the optical rotations of the individual components in the reaction mixture are independent of each other and that the observed rotation of the reaction, α_t, at time t is given by Equation (25) (1),

$$\alpha_t = \sum_{1}^{i} \alpha_i, \qquad (25)$$

where α_i is the optical rotation due to the ith component at time t.

The second assumption of this derivation is that the reaction of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide results only in the formation of cyclohexyl 2-O-acetyl-3,4,6-tri-O-methyl-α- and -β-D-glucopyranoside and 1,2-O-(1-cyclohexoxyethylidene)-3,4,6-tri-O-methyl-α-D-glucopyranose. Since cyclohexanol is optically inactive, Equation (25) may be written as

$$\alpha_t = \alpha_H + \alpha_a + \alpha_b + \alpha_c, \qquad (26)$$

where α_H = the optical rotation due to the glucosyl bromide at time t

α_a = the optical rotation due to the α-anomeric glucoside at time t

α_b = the optical rotation due to the β-anomeric glucoside at time t

α_c = the optical rotation due to the orthoester at time t

The optical rotation due to the ith component at time t is given by Equation (27) (1),

$$\alpha_i = C_i \ell [m_i], \tag{27}$$

where C_i = the concentration of the ith component (mole/liter)

ℓ = the solution path length of the plane-polarized light (dm)

$[m_i]$ = the molar specific optical rotation of the ith component [(degree)(liter)/(dm)(mole)]

If P is defined as the total product concentration and n_a, n_b, and n_c are defined as the mole fraction of α-anomeric glucoside, β-anomeric glucoside, and orthoester, respectively, then Equations (26) and (27) yield

$$\alpha_t = \alpha_H + n_a P \ell [m_a] + n_b P \ell [m_b] + n_c P \ell [m_c] \tag{28}$$

Let

$$a = \ell [m_a], \tag{29}$$

$$b = \ell [m_b], \text{ and} \tag{30}$$

$$c = \ell [m_c] \tag{31}$$

Substituting Equations (29), (30), and (31) into Equation (28) yields

$$\alpha_t = \alpha_H + a n_a P + b n_b P + c n_c P \tag{32}$$

From stoichiometry,

$$P = H_o - H, \tag{33}$$

where H_o = the initial glucosyl bromide concentration

H = the concentration of glucosyl bromide at time t

For the glucosyl bromide, $\ell [m_i]$ of Equation (27) can be shown to be equal to the initial optical rotation of the reaction system divided by the initial glucosyl bromide concentration. Thus, for the glucosyl bromide Equation (27) can be written as

$$\alpha_H = \alpha_o H/H_o, \tag{34}$$

where α_o is the initial optical rotation of the reaction system (determined by extrapolating to time zero). Substituting Equations (33) and (34) into Equation (32) yields

$$\alpha_t = \alpha_o H/H_o + an_a(H_o - H) + bn_b(H_o - H) + cn_c(H_o - H) \tag{35}$$

Let
$$M = H_o(an_a + bn_b + cn_c) \tag{36}$$

Substituting Equation (36) into Equation (35) and rearranging yields

$$H = H_o(\alpha_t - M)(\alpha_o - M)^{-1}, \tag{37}$$

which relates the optical rotation of the reaction system to the concentration of glucosyl bromide in the reaction mixture at time t.

The molar rotation of a compound can be related to the specific optical rotation of the compound by Equation (38) (1),

$$[m_i] = [\alpha_i]M_i/1000, \tag{38}$$

where $[\alpha_i]$ = the specific optical rotation of the ith compound in the reaction system

M_i = the gram-molecular weight of the ith compound in the reaction system

Substituting Equations (29), (30), (31), and (38) into Equation (36) and rearranging yields

$$M = (H_o M_G/1000)(n_a[\alpha_a] + n_b[\alpha_b]) + (H_o M_{OE}/1000)(n_c[\alpha_c]), \tag{39a}$$

where M_G = the gram-molecular weight of the glucoside

$\underline{M}_{OE}$ = that of the orthoester

$[\alpha_{\underline{a}}]$ = the specific optical rotation of the α-anomeric glucoside

$[\alpha_{\underline{b}}]$ = that of the β-anomeric glucoside

$[\alpha_{\underline{c}}]$ = that of the orthoester

Since $\underline{M}_{\underline{G}}$ equals $\underline{M}_{OE}$, Equation (44) simplifies to

$$M = (H_o M_G/1000)(n_a[\alpha_a] + n_b[\alpha_b] + n_c[\alpha_c]) \qquad (39b)$$

APPENDIX IV

POLARIMETRIC DATA FOR THE 2,3,4,6-TETRA-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE REACTIONS

This appendix contains the polarimetric data for reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide. The data were used in conjunction with Equation (16) to calculate the initial rates of the reactions. The computed value of the initial rate is given for each reaction. Optical rotations were measured on a Perkin Elmer 141 MC polarimeter using a mercury lamp at 546.1 nm.

TABLE XXXV

REACTION NO 14: GLUCOSYL BROMIDE, 5.862×10^{-3}M; CYCLOHEXANOL, 9.024×10^{-2}M; MERCURIC CYANIDE, 5.984×10^{-3}M; TEMP, 10.2°C; $(dH/dt)_{t=0}$, 1.742×10^{-6}MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.25	0.543	3.00	0.523	5.50	0.479	11.00	0.218
1.50	0.541	3.25	0.521	6.00	0.467	13.00	0.115
1.75	0.539	3.50	0.518	6.50	0.455	15.00	0.070
2.00	0.536	3.75	0.514	7.00	0.440	17.00	0.059
2.25	0.534	4.00	0.510	8.00	0.395	19.00	0.053
2.25	0.531	4.50	0.500	9.00	0.343	α_∞	0.032
2.75	0.529	5.00	0.490	10.00	0.280		

TABLE XXXVI

REACTION NO. 15: GLUCOSYL BROMIDE, 3.205×10^{-3}M; CYCLOHEXANOL, 8.760×10^{-2}M; MERCURIC CYANIDE, 6.061×10^{-3}M; TEMP, 10.1°C; $(dH/dt)_{t=0}$, 8.479×10^{-7}MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.25	0.311	4.00	0.295	6.75	0.297	14.00	0.206
1.50	0.310	4.25	0.294	7.00	0.276	15.00	0.194
1.75	0.308	4.50	0.292	7.50	0.273	17.00	0.163
2.00	0.307	4.75	0.292	8.00	0.270	19.00	0.132
2.25	0.306	5.00	0.290	8.50	0.265	21.00	0.105
2.50	0.305	5.25	0.289	9.00	0.262	25.00	0.066
2.75	0.304	5.50	0.285	9.50	0.257	27.00	0.058
3.00	0.303	5.75	0.286	10.00	0.253	30.00	0.048
3.25	0.302	6.00	0.285	11.00	0.244	α_∞	0.028
3.50	0.289	6.25	0.282	12.00	0.231		
3.75	0.296	6.50	0.280	13.00	0.219		

TABLE XXXVII

REACTION NO. 16: GLUCOSYL BROMIDE, 6.200×10^{-3}M; CYCLOHEXANOL, 4.519×10^{-2}M; MERCURIC CYANIDE, 6.122×10^{-3}M; TEMP, 10.2°C; $(dH/dt)_{t=0}$, 1.826×10^{-6}MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.566	3.00	0.547	6.00	0.504	12.00	0.295
1.25	0.563	3.25	0.545	6.50	0.494	13.00	0.248
1.50	0.561	3.50	0.542	7.00	0.484	14.00	0.205
1.75	0.559	3.75	0.538	7.50	0.471	16.00	0.142
2.00	0.557	4.00	0.535	8.00	0.457	18.00	0.112
2.25	0.554	4.50	0.529	9.00	0.427	22.00	0.090
2.50	0.552	5.00	0.520	10.00	0.387	α_∞	0.062
2.75	0.550	5.50	0.512	11.00	0.344		

TABLE XXXVIII

REACTION NO. 17: GLUCOSYL BROMIDE, 6.076×10^{-3}M; CYCLOHEXANOL, 13.281×10^{-2}M; MERCURIC CYANIDE, 5.938×10^{-3}M; TEMP, 10.0°C; $(dH/dt)_{t=0}$, 1.786×10^{-6}MOLExLIT^{-1}SEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.549	2.75	0.529	5.00	0.480	10.00	0.163
1.25	0.546	3.00	0.523	5.50	0.463	11.00	0.101
1.50	0.544	3.25	0.519	6.00	0.445	13.00	0.046
1.75	0.542	3.50	0.514	6.50	0.422	15.00	0.033
2.00	0.539	3.75	0.510	7.00	0.396	α_∞	0.019
2.25	0.537	4.00	0.505	8.00	0.329		
2.50	0.533	4.50	0.493	9.00	0.240		

TABLE XXXIX

REACTION NO. 18: GLUCOSYL BROMIDE, 6.052×10^{-3}M; CYCLOHEXANOL, 9.068×10^{-2}M; MERCURIC CYANIDE, 3.134×10^{-3}M; TEMP, 10.2°C; $(dH/dt)_{t=0}$, 8.741×10^{-7}MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.579	2.75	0.570	5.00	0.556	10.00	0.490
1.25	0.577	3.00	0.569	5.50	0.549	11.00	0.400
1.50	0.576	3.25	0.567	6.00	0.546	12.00	0.320
1.75	0.575	3.50	0.565	6.50	0.538	13.00	0.231
2.00	0.574	3.75	0.564	7.00	0.532	15.00	0.090
2.25	0.572	4.00	0.562	8.00	0.515	17.00	0.047
2.50	0.570	4.50	0.559	9.00	0.490	19.00	0.042
						α_∞	0.033

TABLE XL

REACTION NO. 19: GLUCOSYL BROMIDE, 6.981×10^{-3}M; CYCLOHEXANOL, 9.175×10^{-2}M; MERCURIC CYANIDE, 12.116×10^{-3}M; TEMP, 10.1°C; $(dH/dt)_{t=0}$, 3.448×10^{-6}MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.623	2.75	0.580	5.00	0.440	10.00	0.130
1.25	0.618	3.00	0.559	5.50	0.426	11.00	0.097
1.50	0.614	3.25	0.544	6.00	0.402	13.00	0.085
1.75	0.610	3.50	0.527	6.50	0.530	15.00	0.080
2.00	0.605	3.75	0.513	7.00	0.313	α_∞	0.054
2.25	0.598	4.00	0.492	8.00	0.232		
2.50	0.591	4.50	0.462	9.00	0.177		

TABLE XLI

REACTION NO. 20: GLUCOSYL BROMIDE, 2.598×10^{-3}M; CYCLOHEXANOL, 6.718×10^{-2}M; MERCURIC CYANIDE, 2.222×10^{-3}M; TEMP, 20.0°C; $(dH/dt)_{t=0}$, 5.030×10^{-7}MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.234	3.50	0.228	6.00	0.221	14.00	0.159
1.25	0.234	3.75	0.228	6.50	0.220	16.00	0.127
1.50	0.233	4.00	0.227	7.00	0.216	18.00	0.084
1.75	0.233	4.25	0.226	7.50	0.216	20.00	0.066
2.00	0.232	4.50	0.226	8.00	0.211	23.00	0.047
2.25	0.231	4.75	0.226	8.50	0.211	26.00	0.040
2.50	0.231	5.00	0.224	9.00	0.207	α_∞	0.026
2.75	0.230	5.25	0.224	10.00	0.201		
3.00	0.229	5.50	0.223	11.00	0.193		
3.25	0.229	5.75	0.222	12.00	0.185		

TABLE XLII

REACTION NO. 21: GLUCOSYL BROMIDE, 1.880×10^{-3}M; CYCLOHEXANOL, 4.951×10^{-2}M; MERCURIC CYANIDE, 1.835×10^{-3}M; TEMP, 20.0°C; $(dH/dt)_{t=0}$, 3.007×10^{-7}MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.185	3.75	0.181	6.50	0.175	13.00	0.161
1.25	0.185	4.00	0.181	6.75	0.176	14.00	0.155
1.50	0.185	4.25	0.180	7.00	0.175	16.00	0.149
1.75	0.184	4.50	0.180	7.50	0.174	18.00	0.135
2.00	0.184	4.75	0.179	8.00	0.172	20.00	0.132
2.25	0.183	5.00	0.179	8.50	0.172	22.00	0.150
2.50	0.183	5.25	0.179	9.00	0.171	24.00	0.086
2.75	0.183	5.50	0.178	9.50	0.170	26.00	0.068
3.00	0.182	5.75	0.177	10.00	0.168	28.00	0.055
3.25	0.182	6.00	0.177	11.00	0.167	32.00	0.040
3.50	0.181	6.25	0.177	12.00	0.163	α_∞	0.024

TABLE XLIII

REACTION NO. 22: GLUCOSYL BROMIDE, 3.130×10^{-3}M; CYCLOHEXANOL, 6.808×10^{-2}M; MERCURIC CYANIDE, 2.367×10^{-3}M; TEMP, 15.1°C; $(dH/dt)_{t=0}$, 4.657×10^{-7} MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.300	3.25	0.295	6.00	0.288	12.00	0.258
1.25	0.300	3.50	0.294	6.50	0.286	13.00	0.249
1.50	0.299	3.75	0.293	7.00	0.284	14.00	0.239
1.75	0.299	4.00	0.293	7.50	0.284	16.00	0.211
2.00	0.298	4.25	0.292	8.00	0.281	18.00	0.173
2.25	0.298	4.50	0.292	8.50	0.279	20.00	0.128
2.50	0.297	4.75	0.291	9.00	0.275	22.00	0.086
2.75	0.296	5.00	0.291	10.00	0.270	25.00	0.054
3.00	0.296	5.50	0.290	11.00	0.264	28.00	0.044
						α_∞	0.030

TABLE XLIV

REACTION NO. 23: GLUCOSYL BROMIDE, 1.664×10^{-3}M; CYCLOHEXANOL, 4.542×10^{-2}M; MERCURIC CYANIDE, 1.499×10^{-3}M; TEMP, 15.0°C. $(dH/dt)_{t=0}$, 1.457×10^{-7} MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.140	4.75	0.137	8.50	0.135	18.00	0.128
1.25	0.139	5.00	0.137	8.75	0.135	19.00	0.127
1.50	0.140	5.25	0.137	9.00	0.135	20.00	0.126
1.75	0.140	5.50	0.137	9.50	0.134	22.00	0.124
2.00	0.139	5.75	0.137	10.00	0.134	24.00	0.122
2.25	0.139	6.00	0.137	10.50	0.134	26.00	0.120
2.50	0.139	6.25	0.136	11.00	0.133	28.00	0.117
2.75	0.139	6.50	0.136	11.50	0.133	30.00	0.114
3.00	0.138	6.75	0.136	12.00	0.133	32.00	0.110
3.25	0.139	7.00	0.136	12.50	0.132	37.00	0.100
3.50	0.138	7.25	0.136	13.00	0.132	45.00	0.077
3.75	0.138	7.50	0.136	14.00	0.131	52.00	0.056
4.00	0.137	7.75	0.135	15.00	0.130	60.00	0.037
4.25	0.138	8.00	0.135	16.00	0.130	72.00	0.026
4.50	0.138	8.25	0.135	17.00	0.129	α_∞	0.015

TABLE XLV

REACTION NO. 24: GLUCOSYL BROMIDE, 3.411×10^{-3}M; CYCLOHEXANOL, 10.083×10^{-2}M; MERCURIC CYANIDE, 6.433×10^{-3}M; TEMP, 5.4°C; $(dH/dt)_{t=0}$, 7.001×10^{-7} MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.25	0.311	4.75	0.297	8.25	0.279	16.00	0.222
1.50	0.309	5.00	0.297	8.50	0.279	17.00	0.212
1.75	0.310	5.25	0.295	8.75	0.278	18.00	0.201
2.00	0.308	5.50	0.295	9.00	0.275	19.00	0.189
2.25	0.307	5.75	0.293	9.50	0.272	20.00	0.175
2.25	0.306	6.00	0.294	10.00	0.269	22.00	0.151
2.75	0.305	6.25	0.291	10.50	0.266	24.00	0.126
3.00	0.304	6.50	0.291	11.00	0.266	26.00	0.102
3.25	0.304	6.75	0.290	11.50	0.259	28.00	0.082
3.50	0.303	7.00	0.287	12.00	0.255	30.00	0.065
3.75	0.302	7.25	0.285	12.50	0.252	32.00	0.053
4.00	0.301	7.50	0.283	13.00	0.248	34.00	0.044
4.25	0.299	7.75	0.282	14.00	0.240	36.00	0.038
4.50	0.299	8.00	0.280	15.00	0.232	α_∞	0.019

TABLE XLVI

REACTION NO. 25: GLUCOSYL BROMIDE, 5.756×10^{-3}M; CYCLOHEXANOL, 9.097×10^{-2}M; MERCURIC CYANIDE, 5.967×10^{-3}M; TEMP, 5.2°C; $(dH/dt)_{t=0}$, 1.275×10^{-6} MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.25	0.524	4.00	0.506	6.75	0.482	12.00	0.394
1.50	0.523	4.25	0.505	7.00	0.480	13.00	0.367
1.75	0.521	4.50	0.502	7.50	0.475	14.00	0.335
2.00	0.519	4.75	0.501	8.00	0.466	15.00	0.299
2.25	0.518	5.00	0.500	8.50	0.462	16.00	0.261
2.50	0.516	5.25	0.499	9.00	0.456	17.00	0.222
2.75	0.514	5.50	0.498	9.50	0.447	19.00	0.510
3.00	0.513	5.75	0.496	10.00	0.438	21.00	0.101
3.25	0.511	6.00	0.493	10.50	0.428	23.00	0.074
3.50	0.509	6.25	0.488	11.00	0.418	25.00	0.061
3.75	0.508	6.50	0.485	11.50	0.406	α_∞	0.030

TABLE XLVII

REACTION NO. 26: GLUCOSYL BROMIDE, 2.676×10^{-3}M; CYCLOHEXANOL, 9.159×10^{-2}M; MERCURIC CYANIDE, 2.993×10^{-3}M; TEMP, 1.9°C; $(dH/dt)_{t=0}$, 1.748×10^{-7} MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.50	0.260	10.50	0.251	27.00	0.226	45.00	0.156
2.50	0.259	11.50	0.250	29.00	0.222	50.00	0.120
3.50	0.258	13.00	0.248	31.00	0.218	55.00	0.084
4.50	0.257	15.00	0.245	33.00	0.212	60.00	0.054
5.50	0.256	17.00	0.243	35.00	0.206	65.00	0.032
6.50	0.255	19.00	0.240	37.00	0.198	70.00	0.025
7.50	0.254	21.00	0.238	39.00	0.190	79.00	0.020
8.50	0.253	23.00	0.235	41.00	0.180	α_∞	0.008
9.50	0.252	25.00	0.231	43.00	0.169		

TABLE XLVIII

REACTION NO. 27: GLUCOSYL BROMIDE, 7.849×10^{-3}M; CYCLOHEXANOL, 11.403×10^{-2}M; MERCURIC CYANIDE, 6.438×10^{-3}M; TEMP, 1.9°C; $(dH/dt)_{t=0}$, 1.277×10^{-6} MOLExLIT^{-1}xSEC^{-1}.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.732	3.50	0.713	6.00	0.681	10.00	0.563
1.25	0.730	3.75	0.711	6.25	0.677	11.00	0.509
1.50	0.729	4.00	0.708	6.50	0.672	12.00	0.440
1.75	0.727	4.25	0.704	6.75	0.667	13.00	0.360
2.00	0.725	4.50	0.701	7.00	0.662	14.00	0.274
2.25	0.723	4.75	0.698	7.50	0.650	16.00	0.133
2.50	0.722	5.00	0.695	8.00	0.638	18.00	0.065
2.75	0.720	5.25	0.692	8.50	0.623	20.00	0.044
3.00	0.718	5.50	0.689	9.00	0.606	α_∞	0.019
3.25	0.716	5.75	0.685	9.50	0.584		

TABLE XLIX

REACTION NO. 28: GLUCOSYL BROMIDE, 2.948×10^{-3}M; CYCLOHEXANOL, 4.508×10^{-2}M; MERCURIC BROMIDE, 2.993×10^{-3}M; TEMP, 10.1°C.

t,min	α_t	t,min	α_t	t,min	α_t	t,min	α_t
1.00	0.163	2.50	0.106	4.00	0.083	7.00	0.062
1.25	0.149	2.75	0.102	4.50	0.078	8.00	0.056
1.50	0.137	3.00	0.097	5.00	0.072	9.00	0.053
1.75	0.127	3.25	0.093	5.50	0.070	10.00	0.048
2.00	0.120	3.50	0.089	6.00	0.066	12.00	0.045
2.25	0.112	3.75	0.086	6.50	0.063	α_∞	0.026

APPENDIX V

DERIVATION OF THE EQUATION RELATING THE OPTICAL ROTATION OF THE REACTION MIXTURE TO THE CONCENTRATION OF GLUCOSYL BROMIDE AT TIME *t* FOR THE 2,3,4,6-TETRA-*O*-METHYL-α-D-GLUCOPYRANOSYL BROMIDE REACTION

If it is assumed, as previously (Appendix III) described, that the optical rotation of the individual components in a reaction mixture are independent of each other, the observed rotation of the reaction, α_t, at time *t* is given by

$$\alpha_t = \sum_{1}^{i} \alpha_i, \tag{25}$$

where α_i is the optical rotation due to the *i*th component at time *t*.

The second assumption of this derivation is that the reaction of the 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide results only in the formation of cyclohexyl 2,3,4,6-tetra-*O*-methyl-α- and -β-D-glucopyranoside. Since the cyclohexanol is optically inactive, Equation (25) may be written as

$$\alpha_t = \alpha_H + \alpha_a + \alpha_b, \tag{40}$$

where α_H = the optical rotation due to the glucosyl bromide at time *t*

α_a = the optical rotation due to the α-anomeric glucoside at time *t*

α_b = the optical rotation due to the β-anomeric glucoside at time *t*

The optical rotation due to the *i*th component at time *t* is given by

$$\alpha_i = C_i \ell [m_i], \tag{27}$$

where C_i = the concentration of the *i*th component (mole/liter)

$\underline{\ell}$ = the solution path length of plane polarized light (dm)

$[\underline{m_i}]$ = the molar specific optical rotation of the $\underline{i}$th component [(degree)(liter)/(dm)(mole)]

If $\underline{G}$ is defined as the total glucoside concentration and $\underline{n}$ is defined as the mole fraction of β-anomer in the glucosidic product, then the concentration of β-anomeric glucoside is given by Equation (41) and the concentration of α-anomeric glucoside is given by Equation (42),

$$G_b = nG \tag{41}$$

$$G_a = (1 - n)G \tag{42}$$

Substituting Equations (27), (41), and (42) into Equation (40) yields

$$\alpha_t = \alpha_H + nG\ell[m_b] + (1 - n)G\ell[m_a] \tag{43}$$

where $[\underline{m_b}]$ = the molar rotation of the β-anomeric glucoside

$[\underline{m_a}]$ = the molar rotation of the α-anomeric glucoside

Let

$$a = \ell[m_a] \text{ and} \tag{44}$$

$$b = \ell[m_b] \tag{45}$$

Substituting Equations (44) and (45) into Equation (43) yields

$$\alpha_t = \alpha_H + nbG + (1 - n)aG \tag{46}$$

From stoichiometry,

$$G = H_o - H, \tag{47}$$

where $\underline{H_o}$ = the initial concentration of the glucosyl bromide

$\underline{H}$ = the concentration of glucosyl bromide at time $\underline{t}$

For the glucosyl bromide, $\underline{\ell}[\underline{m_i}]$ of Equation (27) can be shown to be equal to the initial optical rotation of the reaction system divided by the initial bromide concentration. Thus, for the glucosyl bromide Equation (27) can be written as

$$\alpha_H = \alpha_o H/H_o \ , \tag{34}$$

where α_o is the initial optical rotation of the reaction system (determined by extrapolating $\alpha_{\underline{t}}$ to time zero).

Substituting Equations (47) and (34) into Equation (46) yields

$$\alpha_t = \alpha_o H/H_o + nb(H_o - H) + (1 - n)a(H_o - H) \tag{48}$$

Let

$$M = H_o nb + H_o(1 - n)a \tag{49}$$

Substituting Equation (49) into Equation (48) and rearranging yields

$$H = H_o(\alpha_t - M)(\alpha_o - M)^{-1}, \tag{50}$$

which relates the optical rotation of the reaction mixture to the concentration of glucosyl bromide in the reaction mixture at time $\underline{t}$.

The molar rotation of a compound can be related to the specific optical rotation of the compound by Equation (38) ($\underline{1}$):

$$[m_i] = [\alpha_i]M_i/1000, \tag{38}$$

where $[\underline{\alpha_i}]$ = the specific optical rotation of the $\underline{i}$th compound in the reaction system

$\underline{M_i}$ = the gram-molecular weight of the $\underline{i}$th compound in the reaction system

Substituting Equations (44), (45), and (38) into Equation (49) and rearranging yields

$$M = l(n[\alpha_b] + (1 - n)[\alpha_a])M_G H_o/1000, \qquad (51)$$

where $[\alpha_b]$ = the specific optical rotation of the β-anomeric glucoside

$[\alpha_a]$ = the specific optical rotation of the α-anomeric glucoside

M_G = the gram-molecular weight of the glucosic product

APPENDIX VI

PRODUCT ANALYSES FOR REACTIONS OF 2,3,4,6-TETRA-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE

The mole fraction of α-anomer in the glucosidic products, as a function of time, for the reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide with cyclohexanol in the presence of mercuric cyanide in which various reaction temperatures, cyclohexanol concentrations, mercuric cyanide concentrations, and glucosyl bromide concentrations were employed are given in Table L.

The final product analyses of the reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide which were conducted in the kinetic study are given in Table LI. The reaction samples, from which these product distributions were determined, were obtained after long reaction times.

TABLE L

ANOMERIC GLUCOSIDE ANALYSES AS A FUNCTION OF TIME FOR THE REACTIONS OF 2,3,4,6-TETRA-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE EMPLOYING VARIOUS CONCENTRATIONS OF REACTANTS

Temp., °C	Glucosyl Bromide (10^3M)	Cyclohexanol (10^2M)	$Hg(CN)_2$ (10^3M)	Time, min	Reaction, %[a]	Mole Fraction, α-anomer[b]
20	7.134	9.519	6.019	2.1	17	0.24
				3.0	26	0.25
				4.1	49	0.25
				4.9	72	0.24
				6.0	91	0.25
				8.1	96	0.24
					100	0.26
10	5.862	9.024	5.984	2.8	5	0.23
				4.2	9	0.24
				5.2	13	0.24
				6.2	18	0.22
				7.8	29	0.23
					100	0.23
10	6.671	4.639	5.921	2.1	3	0.30
				3.1	5	0.29
				4.1	8	0.28
				5.1	12	0.28
				6.0	16	0.29
				8.2	33	0.27
					100	0.29
10	3.205	8.760	6.061	2.8	6	0.25
				3.9	7	0.25
				6.0	12	0.23
				8.5	17	0.23
					100	0.24
10	6.052	9.068	3.134	4.0	4	0.26
				4.9	5	0.26
				6.3	8	0.24
				8.2	14	0.24
					100	0.24

[a] Calculated from the polarimetric data (Appendix IV) and Equation (16).

[b] Mole fraction of cyclohexyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside in the glucosidic product.

TABLE LI

FINAL PRODUCT ANALYSES FOR REACTIONS OF 2,3,4,6-TETRA-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE CONDUCTED IN THE KINETIC STUDY[a]

Reaction Number[b]	Glucosyl Bromide (10^3M)	Cyclohexanol (10^2M)	$Hg(CN)_2$ (10^3M)	Temp., °C	Glucosides, %[c]	n_α[d]	Reducing Sugar, %[c]	Total Yield, %[e]
14	5.862	9.024	5.984	10.2	93	0.23	3	97
15	3.205	8.760	6.061	10.1	96	0.23	3	98
16	6.200	4.519	6.122	10.2	101	0.27	5	106
17	6.076	13.281	5.938	10.0	91	0.18	3	94
18	6.025	9.068	3.134	10.2	97	0.22	5	101
19	6.981	9.175	12.116	10.1	90	0.21	3	93
20	2.598	6.718	2.222	20.0	89	0.27	3	92
21	1.880	4.951	1.835	20.0	101	0.30	4	105
22	3.130	6.808	2.367	15.1	97	0.23	4	101
23	1.664	4.542	1.499	15.0	98	0.30	5	103
24	3.411	10.083	6.433	5.4	100	0.17	1	101
25	5.756	9.097	5.967	5.2	92	0.18	4	96
26	2.676	9.159	2.993	1.9	94	0.18	3	97
27	7.849	11.403	6.438	1.9	90	0.17	2	92
28	2.948	4.508	(2.993)[f]	10.1	96	0.24	2	98

[a] GLC product analyses of reaction samples obtained after long reaction times.

[b] Reaction numbers correspond to polarimetric data given in Appendix IV.

[c] Based on the theoretical yield.

[d] The mole fraction of α-anomeric glucoside in the glucosidic product. Analyses of samples containing known concentrations of α- and β-anomeric glucosides indicated that the mole fraction of α-anomer in the glucosidic product could be determined within ±2 mole%.

[e] Total yield of glucosides and reducing sugar based on the theoretical yield.

[f] Mercuric bromide was used in place of mercuric cyanide.

APPENDIX VII

METHOD FOR CALCULATING THE THERMODYNAMIC FUNCTIONS OF ACTIVATION

The thermodynamic functions of activation for the reactions of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide and the 2-O-acetyl analog were calculated as follows: The Arrhenius energy of activation (E_a) was determined from the slope of the Arrhenius correlation which is based on the logarithmic form of the Arrhenius equation [Equation (52b)]:

$$k_r = A \exp(-E_a/RT), \tag{52a}$$

$$\ln k_r = \ln A - E_a/RT, \tag{52b}$$

where k_r = the rate constant, sec^{-1}

A = the "frequency factor" (emperical correlation coefficient)

R = gas constant, 1.9865 cal $°K^{-1}$ $mole^{-1}$

T = temperature, °K

The enthalpy of activation ($\Delta H^{\ddagger}$) was calculated from Equation (53) (48):

$$\Delta H^{\ddagger} = E_a - RT + p\Delta v^{\ddagger}, \tag{53}$$

where $p\Delta v^{\ddagger}$ approximately equals zero, since $\Delta v^{\ddagger}$, the volume change in the reaction, is virtually zero for these glucosyl bromide reactions.

The entropy of activation ($\Delta S^{\ddagger}$) was calculated from Equation (55) which is derived from Equation (54) and Equation (52a). Equation (54), derived from the theory of absolute reaction rates (48), relates the free energy of activation to the specific rate constant.

$$k_r = (ekT/h) \exp(-E_a/RT) \exp(\Delta S^{\ddagger}/R), \quad (54)$$

where e = base for Napierian logarithms, 2.7183

k = Boltzmann constant, 1.380×10^{-16} erg deg^{-1}

h = Planck constant, 6.625×10^{-27} erg sec

$$\Delta S^{\ddagger} = R \ln (A/T) + R \ln (h/ek)$$
$$= 1.987 \ln (A/T) - 49.2 \quad (55)$$

The free energy of activation was calculated from Equation (56):

$$\Delta F^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \quad (56)$$

APPENDIX VIII

GLC MOLAR RESPONSE FACTORS USED IN ANALYSES OF REACTIONS OF 2-O-ACETYL-3,4,6-TRI-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE

Chloroform solutions of the compounds in Table LII were treated according to Procedure A[1]. GLC, Conditions A and B, resulted in the response factors in Table LIII.

TABLE LII

SOLUTION COMPOSITION FOR RESPONSE FACTOR DETERMINATION

Solution Number	Mole Ratio of Internal Standard[a]						
	OE	β-Cyc 2-OAc	α-Cyc 2-OAc	β-Cyc 2-OH	α-Cyc 2-OH	TMG	Phenyl 1-S-2-OAc
1	0.68	3.78	5.22	6.67	16.28	7.20	0.98
2	0.38	0.85	2.91	1.79	3.64	1.61	0.54
3	1.14	1.26	8.70	2.86	4.63	1.30	1.63
4	1.32	0.73	10.07	1.55	3.15	1.11	1.88
5	3.42	0.76	26.12	1.00	3.26	0.96	4.88

[a] Internal standard: ethyl 3,4,6-tri-O-methyl-2-O-propionyl-β-D-glucopyranoside. See Nomenclature for compound names.

[1] Described in the Experimental section under Quantitative Measurement Procedures for the reaction of the 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucopyranosyl bromide study.

TABLE LIII

GLC MOLAR RESPONSE FACTORS ($f_{\underline{x}}$[a]) RELATIVE TO ETHYL 3,4,6-TRI-O-METHYL-2-O-PROPIONYL-β-D-GLUCOPYRANOSIDE

Solution Number	$f_{\underline{x}}$[a] OE		β-Cyc 2-OAc	α-Cyc 2-OAc	β-Cyc 2-OH	α-Cyc 2-OH	TMG	Phenyl 1-S-2-OAc
1	0.97	--	1.40	1.31	1.44	1.46	1.06	1.45
	0.95	--	1.41	1.35	1.49	1.56	1.07	1.45
2	0.90	0.74[b]	1.41	1.24	1.45	1.37	1.09	1.46
	0.90	0.76	1.42	1.24	1.45	1.38	1.09	1.47
3	0.88	0.76[b]	1.45	1.40	1.51	1.37	1.05	1.46
	0.87	0.78	1.44	1.30	1.48	1.44	1.06	1.45
4	0.90	0.73[b]	1.40	1.45	1.46	1.37	1.09	1.45
	0.88	0.74	1.39	1.42	1.48	1.40	1.09	1.49
5	0.90	0.71[b]	1.35	1.41	1.40	1.31	0.98	1.42
	0.89	0.72	1.39	1.36	1.42	1.35	0.98	1.44
Av. $f_{\underline{x}}$	0.90	0.74	1.41	1.35	1.46	1.40	1.06	1.45

[a] $f_{\underline{x}}$ = (Area X/Area standard)(Mole standard/Moles X); see Nomenclature for compound names.

[b] GLC molar response factor of the orthoester using GLC Conditions B. All other response factors given in this table were calculated using Conditions A.

The moles of each component identified and measured by GLC were calculated by the use of Equation (57):

$$\text{Moles X} = (1/f_x)(\text{Area X/Area standard})(\text{Moles standard}), \qquad (57)$$

where $f_{\underline{x}}$ = the GLC mole response factor of Component X relative to the internal standard (Table LIII)

Area X = GLC response of Component X

Area standard = GLC response of the internal standard

Moles standard = moles of internal standard in the sample

APPENDIX IX

GLC MOLAR RESPONSE FACTORS USED IN ANALYSES OF REACTIONS OF 2,3,4,6-TETRA-O-METHYL-α-D-GLUCOPYRANOSYL BROMIDE

Chloroform solutions of the compounds in Table LIV were prepared. GLC analysis (Conditions C) of the solutions resulted in the response factors in Table LV.

TABLE LIV

SOLUTION COMPOSITION FOR RESPONSE FACTOR DETERMINATION

Solution Number	Mole Ratio of Internal Standard[a]			
	1-O-Propionyl T_4MG	β-Cyc T_4MG	α-Cyc T_4MG	Phenyl 1-S T_4MG
1	9.73	0.35	3.36	0.48
2	4.94	0.44	2.79	0.60
3	2.25	0.54	2.10	0.79
4	3.53	0.46	1.29	1.01
5	2.74	0.65	1.16	2.01

[a]Internal standard: n-butyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside. See Nomenclature for compound names.

The moles of each component identified and measured by GLC were calculated by the use of Equation (57) (Appendix VIII). Equation (57) was employed in the analysis of the chromatograms resulting from the samples in which only the mole fraction of cyclohexyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside in the glucosidic products was determined, e.g., Table L.

TABLE LV

GLC MOLAR RESPONSE FACTORS ($\underline{f}_{\underline{x}}^{a}$) RELATIVE TO n-BUTYL 2,3,4,6-TETRA-O-METHYL-β-D-GLUCOPYRANOSIDE

Solution Number	$\underline{f}_{\underline{x}}^{a}$ 1-O-Propionyl T_4MG	β-Cyc T_4MG	α-Cyc T_4MG	Phenyl 1-S T_4MG
1	0.49	1.26	1.19	1.10
	0.45	1.24	1.19	1.10
2	0.44	1.25	1.21	1.09
	0.48	1.26	1.21	1.12
3	0.44	1.25	1.16	1.09
	0.47	1.24	1.18	1.10
4	0.49	1.24	1.17	1.09
	0.48	1.25	1.18	1.11
5	0.48	1.26	1.17	1.08
	0.45	1.24	1.19	1.08
Av. $\underline{f}_{\underline{x}}$	0.47	1.25	1.18	1.10

[a] $\underline{f}_{\underline{x}}$ = (Area X/Area standard)(Moles standard/Moles X); see Nomenclature for compound names.

$$n_{\alpha} = (\text{Area } \alpha/f_{\alpha})/[(\text{Area } \alpha/f_{\alpha}) + (\text{Area } \beta/f_{\beta})] \qquad (58)$$

where $\underline{n}_{\underline{\alpha}}$ = the mole fraction of the α-anomeric glucoside in the glucosidic product

Area α = the GLC response of the α-anomeric glucoside

$\underline{f}_{\underline{\alpha}}$ = the GLC response factor for the α-anomeric glucoside relative to the internal standard (Table LV)

Area β = the GLC response of the β-anomeric glucoside

$\underline{f}_{\underline{\beta}}$ = the GLC response factor for the β-anomeric glucoside relative to the internal standard (Table LV)